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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY 1940

TREATMENT OF GONADAL HYPOFUNCTION*

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THE DISORDERS of gonad hormone production which have been identified may be considered varieties of reduced function in almost every case. The usual finding in study of any endocrine structure is a group of clinical cases with evidences of deficiency of secretion, another with results attributable to an excess of the hormone, and still other cases with anatomic problems without evidence of any significant deviation from the normal secretory pattern. In the case of the pancreas, diabetes was for many years believed to represent an insulin deficit. The discovery of relatively pure insulin led at an early date to the recognition of a syndrome characteristic of excessive insulin production. In the case of gonadal function the analogy does not yet apply, for we have no clinical conditions which we can be certain represent excessive hormone secretion. Certain neoplasms must remain an exception, but they do not affect this conclusion. Consequently the clinical states subject to examination and treatment in the field of gonad function are endocrine deficiency or hypofunctional syndromes. Employing conventional terms these may be listed as in Table I. It is becoming increas-

* Presented October 24, 1939 at The New York Academy of Medicine in the Twelfth Graduate Fortnight.

TABLE I

CLINICAL STATES SUBJECT TO TREATMENT IN THE FIELD OF GONAD FUNCTION

Male Hypogonadism	*Female Hypogonadism*	
Infantilism	Infantilism	
Froehlich syndrome	Primary amenorrhea	
Cryptorchidism	Froehlich syndrome	
Eunuchoidism	Secondary amenorrhea	
Climacteric	Infrequent menses	
Sterility	Menorrhagia	
	Anovulatory flowing	May occur before or after one or more pregnancies
	Sterility	
	Repeated abortion	
	Climacteric	
	Premature	
	Artificial	
	Spontaneous, normal	

ingly evident that the large number of disorders of menstrual rhythm and of fertility do not represent so many entities, but result from varying relationships among a few biological factors. Attention has been focused on three of these factors that are of predominant significance: production of estrogenic substances by the Graafian follicle, production of progesterone by the corpus luteum, and the maturation and liberation of a mature ovum which normally precedes corpus luteum formation. It will be recognized that the two secretory processes may vary in intensity, duration, or rhythmicality. The biological stimuli necessary for the ovarian cycle have been presented by Evans and Collip[1] in the preceding lectures. Given at least two pituitary gonadotropic factors, two ovarian hormones, and the multitude of incidental biological modifying factors which impinge on this delicately balanced system, it would tax mathematical methods to predict the number of syndromes that might occur with only hypofunction to be considered. It will be profitable to examine in functional terms some of the typical disorders as examples of these generalizations. We know, for example, that we must no longer contrast amenorrhea and menorrhagia as deficiency and excess of ovarian activity, respectively. These are but contrasted types of underactivity of ovaries. Why amenorrhea occurs in one woman or at one time, menorrhagia in another, we do not yet know.

Pathogenesis of Hypogonadal Conditions

From the ancient traditions of clinical medicine to the present era we have recognized the interference with reproductive function which is frequently the sequel of chronic infection or debilitating disease. Whether this operates via the anterior pituitary or the gonads is usually not clear. Perhaps the quantitative methods of measuring the functions of these glands will become adequate to enable future clinical investigators to decide these points. Within the endocrine system itself the results upon ovarian function of adrenal or pancreatic deficiency states are recognized, but not explained. The gynecologist has long been saying that his best endocrine tool is thyroid therapy. This must not be understood to mean that thyroid has a specific gonadotropic effect. The key to this question has been provided by the observations of A. E. Severinghaus[2] that the anterior pituitary is morphologically altered in experimental animals by either thyroidectomy or administered thyroid. The clinician correspondingly finds it important to search for slight thyroid disturbances as one of the possible causes for gonad disorders. Even lacking clinically demonstrable hypothyroidism, it occasionally is found that moderate doses of thyroid have provided a stimulus to some part of the pituitary-gonad system, with relief from amenorrhea, menorrhagia, dysmenorrhea, or sterility. Although it is to be hoped that the improving methods for diagnosis will make this non-specific therapeutic approach less important, at present it remains the method most widely relied upon outside the investigative clinics.

Another question with peculiar problems is presented by variable phenomena of adolescence. The growth in stature, which comes to its maximum during this period, is conditioned by the pituitary which seems to act both directly and via the thyroid and parathyroids.[3] The rapid maturing of sex organs and functions depends on pituitary stimulation. These two processes—growth and maturation—are usually nicely adjusted in time and intensity, with the result which we choose to call normal adult types. But the clinician knows that these two pituitary functions can be dissociated, as shown by the occurrence of sexually mature dwarfs and sexually infantile giants, where one pituitary conditioned process greatly outstrips the other. Furthermore, there is an apparent antagonism between these two processes in one way. When sex maturity is well advanced the union of epiphyses occurs in the last

of the long bones, and further gain in height is forestalled. The explanation of this apparent sex effect on bone maturation is not yet at hand. But the clinician is well advised to concentrate attention on skeletal growth before the epiphyses of the femur unite to make further gain in stature impossible. If intensive gonad stimulation is planned, it should wait. This is merely recognizing in a clinical plan the orderly procedures of nature: final growth is achieved during adolescence and before sexual development is complete. An exception may be made for such a brief period of therapy as may be necessary to induce descent of cryptorchid testes.

Failure of gonadal functions in late adolescence or adult life always presents the problem of differentiating between inability of the gonad to respond and understimulation by the anterior pituitary. Removal of gonads by surgery or irradiation has proved that increased production, secretion, and urinary excretion of pituitary gonadotropic hormone occurs after the removal from the body of the gonadal hormones. This has led to the belief in the inhibition of the pituitary by the gonadal secretion. The quantitative aspects of this inhibition need far more exploration than has yet been reported. With our limited information it is easy to construct theoretical explanations for these disorders beyond our present ability to test the theories, much less to prove them. For example, it is common practice (not in experimentally organized clinics, of course) to administer to the same woman pituitary extracts to stimulate her ovaries and follicular extracts to stimulate her uterus. Current criticism of this procedure is based on belief in the inhibition of pituitary activity by the use of such follicular or estrogenic hormones. Recent results from my laboratory[4] make it appear that relatively enormous doses of estrogen are required to accomplish such inhibition. These results, although obtained in human subjects, are limited to the greatly increased pituitary hormone excretion which occurs in the climacteric. Such findings may not be transferred directly and quantitatively to the reproductive period characterized by lower pituitary activity until the approach of the climacteric exaggeration of this process. It is known that the use of estrogenic hormone in women with regularly recurring menstrual cycles may lead to irregularity. This is prima facie evidence of the sensitivity of the mechanism to estrogen. It is theoretically possible that certain doses, given for brief periods, may act to stimulate secretion or release of a pituitary hormone. So much uncertainty attends this

question, that no recommendations can yet be made except this: when it is desired to stimulate the ovary, avoid the administration of ovarian hormone and employ pituitary gonadotropic extract.

Another aspect of the question of ovarian versus pituitary failure is presented in its most extreme form by secondary amenorrhea. Can the ovary no longer respond adequately, or is its stimulation inadequate? This question cannot be answered by history and physical examination, nor by pelvic examination even when amplified with the study of tissue obtained from endometrium or vaginal mucosa. It is stated that assays of blood and urine for estrogen and gonadotropic hormone will add significant data. With methods usually employed even this is doubtful in many cases. The hormone assay methods are being improved, and, even more important, are being evaluated by studies of normal human subjects. But the clinical decision about ovarian or pituitary responsibility for underfunction of the ovaries must usually be determined by a trial of gonadotropic therapy. If the treatment fails to produce increased ovarian activity, in spite of large doses of active pituitary material, it must be concluded that the ovary is for some reason refractory. Treatment, therefore, seems futile. Such a decision, possibly prejudicial to the patient's future, should be made only after the use of known active gonadotropic extracts and with objective criteria for ovarian activity. This leads to a discussion of the diagnostic techniques and the therapeutic materials.

Diagnostic Techniques

Careful inquiry into the details of menstrual rhythm, fertility, and contraceptive practice still needs to be stressed. A casual assertion of regularity of menses cannot be accepted at face value. The varied picture of rhythm in health, in contrast to the usually asserted "every twenty-eight days", is reported by Engle and Shelesnyak[5] and Fluhmann.[6] But even normal regularity is no guarantee of a fertile cycle marked by ovulation, for some cases of proven anovulatory flowing may occur in cycles of essentially four week type. The details of history will often provide a more profitable lead in the study of a gynecological endocrine problem that can be obtained from the physical examination.

In the history, increasing attention is being devoted to the possible origin of the difficulty shortly after a pregnancy. Except for infantilism

and primary amenorrhea at one extreme and the climacteric at the other, any of the syndromes mentioned in Table I may occur soon after a pregnancy. The pathogenesis of this association may be logically considered in connection with the striking morphological changes in the pituitary during pregnancy. These alterations in anterior lobe cells are usually reversible, but at times there may be enduring residuals. Most striking is the report of infarcts in the anterior lobe following a shock-like picture at delivery. In this connection Sheehan[7] has provided us with human postmortem evidence of glandular alterations which can cause genital failure. It appears probable that less extensive infarcts or other types of damage in this area may be traced with increasing frequency when their possible significance is appreciated. Consequently, we must inquire not only into the time of onset of the gynecological symptoms, but also we must search for other evidences of disturbed anterior pituitary functions and for hypothalamic symptoms. For the latter growing field, reference should be made to the monograph of Ranson.[8]

In conducting a physical examination the details need not be listed here, but the problems of obesity and skeletal development require some comment. I must confess inability to discriminate with any certainty those types of obesity associated with evident pituitary regional disease as opposed to the ones explainable by overeating and inactivity, or by hypoglycemia with its exaggerated hunger. Increasingly I have been convinced that all these gynecological conditions may occur either with or without obesity. When there is obesity we choose to call the hypofunction a Froehlich syndrome. With the recognition of the obesity as a separate factor in the syndrome has come the admission that it must be treated as a problem for dietary control. So far the only way in which pituitary therapy appears to help reduce obesity has been the stimulation to more adult points of view as secondary sex characters have developed, with consequent improved self control in adhering to dietary restrictions.

More important than obesity from a diagnostic point of view is the matter of skeletal proportions. Relationship of span to height has been associated with control by the pituitary growth factors.[9] A distortion from approximate equality in these measurements may give correlative evidence for pituitary disease during juvenile or adolescent years. The relatively narrow shoulders and broad pelvic girdle of the female type

do not appear in the male unless there is a lack of androgenic influence. Conversely broad shoulders and narrow pelvis should make us seek masculinizing factors in a female. At present, inspection is more serviceable than accurate measurements in judging the shoulder and pelvic girdles.

Direct examination of the external genitalia, prostatic palpation, and bimanual pelvic examination must be thorough. When these do not eliminate endocrine problems as of etiologic importance, they may serve to give anatomic information about delayed development. But the examination is incomplete without tissue specimens in most of the endocrine problems. The use of curette or endometrial biopsy instrument is increasing, but it should become still more widespread. Obtaining the specimen of endometrium is to be planned with care as to the time in the menstrual cycle. If it is obtained shortly before the appearance of the flow, or during the first hours of the menses, the absence of the typical progestational changes will justify the diagnosis of failure of ovulation or anovulatory flowing. If the tissue is obtained too early in the cycle one can only speculate about ovulation and corpus luteum formation, and secure an approximation about the intensity of follicular hormone activity from the extent of glandular development.

A more quantitative idea of the intensity of estrogenic effect may be secured from the examination of vaginal mucosa, by biopsy[10] or most simply by the study of smears as described by Papanicolaou and Shorr.[11] Although the vaginal tissue does not contribute definite evidence of progestin action, the type of epithelial cells does indicate the estrin effect with sufficient certainty that one may follow increases from day to day whether estrogen is administered, as in the menopause, or the ovaries are stimulated by gonadotropic hormone to produce more estrogen. It is this technique which makes it possible to determine whether a given therapeutic program has promise, for example in treating amenorrhea.

Widespread enthusiasm for assays of estrogenic and gonadotropic hormones in blood and urine has followed the proved dependability of the Aschheim-Zondek and Friedman tests for pregnancy. The demonstrated accuracy of pregnancy-diagnosis methods does not apply to these methods used in the non-pregnant. This enthusiasm for assays is giving way now to disappointment in many quarters, because of the technical difficulties and cost of the assays, and even more because of the uncertainty of interpretation. This lack of dependability of assay results is probably due to three factors: the methods lack specificity for the hor-

mone in question, they are not sufficiently sensitive to detect the normal amount of hormone day by day, or they have not been studied in enough normal subjects to provide a dependable base line for comparisons with the patients we desire to study. For some time to come this approach must remain a method for the research clinic only. Improvements are being produced rapidly. A method recently published[12] is enabling us to make discriminations between climacteric types and those resulting from pituitary failure. The way in which it can be used will be illustrated.

Therapeutic Materials

The first sex hormones to be employed in the clinic were of the estrogenic group. These are useful for replacement therapy, as in the climacteric, or for temporary effects on the vagina, as in juvenile gonorrheal vaginitis. The relative merits of the different estrogens have been described[13] and will be further discussed by Doctor Shorr.[14] The employment of estrogens to stimulate the pituitary, and secondarily the ovaries, is a theoretical possibility which has not yet been studied sufficiently to allow any suggestions about its use. The attempt to inhibit pituitary overactivity by estrogen therapy in the menopause is probably futile unless the doses are enormously large as compared with those which secure clinical control of the menopausal symptoms.[15]

More recently androgens have been secured in pure form. These are analogous to estrogens for substitution therapy in the male climacteric. They have been employed similarly in the female, with some symptomatic benefit. They exert a powerful inhibitory influence on the anterior pituitary, and hence can suppress ovarian activity markedly. These activities have led to treatment of a variety of gynecological disorders with testosterone. Caution seems urgent because even a slight increase in dose above the amount found necessary has not infrequently led to such masculine changes as beard growth and enlargement of the larynx with voice change. Such phenomena are not easily reversible. Since this androgenic therapy does not achieve results which cannot be accomplished otherwise, it seems at present to be of scientific interest rather than clinical importance in the female.

The hormone of the corpus luteum, progesterone, is of indispensable importance in obtaining the progestational changes in endometrium which must precede nidation of the fertilized ovum and must support

gestation. It is available in several preparations, but the therapeutic effects have been disappointing save in some cases of dysmenorrhea and of repeated abortion. This may be due to inadequate dosage, but it is more probable that mere administration of this hormone to a woman without ovulation and corpus luteum formation is not sufficient to correct the difficulty. The therapy must include gonadotropic material which can add to the normal stimulation of the ovaries by the patient's own gland.

The first of these gonadotropic substances tried was a concentrate from the urine of pregnant women, chorionic gonadotropin, usually spoken of as anterior pituitary-like hormone, A.P.L. A constantly increasing body of evidence justifies the statement that this hormone has as its normal function the maintenance of the corpus luteum of pregnancy, but that in the non-pregnant woman it causes atresia of the Graafian follicles, and does not stimulate the human ovaries to ovulation and the formation of corpora lutea. A most interesting discovery has been that chorionic gonadotropin will stimulate the descent of cryptorchid testes[16] and this has been applied to human therapy with profit. Thompson and Heckel[17] have discussed the dosage, differential diagnosis, and the risks involved.

The extraction from the anterior pituitary itself of gonadotropic materials which could be used clinically began with Hisaw and Fevold,[18] and Collip has added alternative methods.[19] All the pituitary extracts so far available contain at least two gonadotropic substances, called follicle stimulating (F.S.H.) and luteinizing (L.H.) hormones. These occur in varying proportions. Known methods of assay do not allow quantitative determinations of the two when they occur in mixtures. Consequently, we must work at present with mixtures the composition of which we cannot be told. Shortly it will be possible to have extracts of these two hormones in separate solutions for clinical trials. We may anticipate superior results from more accurate prescription to fit the needs. One further handicap to the use of these pituitary extracts is the presence in all commercial products of proteins which are probably of no therapeutic importance but which cause painful local reactions and occasionally allergic manifestations.

The protein content has been greatly reduced in the gonadotropic preparations made from the serum of pregnant mares. This substance is not identical with either the chorionic gonadotropin of women or the

hormones from the anterior lobe itself. However, its physiological effects most nearly resemble the pituitary hormone, and results to be reported are typical of the way in which this hormone may stimulate the human ovaries to ovulation, corpus luteum formation, with improved fertility. The pregnant mare's serum (P.M.S.) contains either two hormones as does the pituitary extract, or its hormone has both types of action. The low protein content of the commercial preparations has made this material safer for intravenous administration of large doses than is the case with the pituitary extracts.[20]

Reference has been made to the use of thyroid therapy in gynecological conditions. It must be emphasized that thyroid is marketed in several types. We can ill afford to use anything but standardized thyroid. General insistence on U.S.P. thyroidea sicca as the only thyroid used would serve to eliminate many differences of opinion about the efficacy of thyroid therapy.

Therapeutic Programs

Since the gonadotropic materials are water-soluble, act quickly and for brief periods only, it is necessary that we employ frequently repeated doses of small or moderate size rather than occasional large injections. An exception occurs in the case of intravenous injection to produce ovulation, as suggested by Hisaw and Foster.[21] For this latter purpose it may be advisable to use smaller doses hypodermically before intravenous injection, to lead to adequate follicle development, and small doses after the large one to sustain the secretory activity of the corpus luteum. The injections of gonadotropic material for this supportive therapy of follicle or corpus luteum are to be given hypodermically. There is no evidence that intramuscular injections are better, and animal experiments suggest that the slower absorption under the skin is desirable.

Because the ovarian cycle of women is marked by variations in the amount of pituitary activity, it seems logical to vary the pituitary therapy in cyclic fashion. The complete rationalization of this cyclic therapy must await quantitative data from assays in any given patient. This we hope to make available in due time. Until then we prefer to employ therapy for stimulation of the follicle during the first two weeks of the menstrual cycle only, to avoid the risk of producing cystic follicles. Hisaw has shown that continuous therapy can do this in the

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monkey.[22] In the most extensive pituitary failure it may be necessary to continue therapy through the entire cycle, but even here it can be varied in its intensity in a cyclic manner.

The control of the size of dose and its frequency may be based on the study of response to treatment, gauged by vaginal smears, occasional endometrial biopsies, observations of developing secondary sex characteristics, growth of external genitalia or uterus, and by the careful recording in graphic fashion of the duration and interval of the menstrual flows. If large doses of gonadotropic extracts fail to give increased evidence of estrogenic activity in the vaginal mucosa in cases of amenorrhea or infantilism, therapy may as well be abandoned.

Allergic reactions, though occasionally seen, have been infrequent, in spite of the protein content of the gonadotropic extracts. Local inflammatory reactions, when severe, may necessitate a change from pituitary to pregnant-mare serum extracts. The development of antihormones under therapy is a puzzling aspect of this program. Elsewhere, Meyer and Sevringhaus[23] are reporting this phenomenon but point out that it does not appear to be a limiting factor in securing results. We are inclined to minimize the importance of antihormones in the clinic.

One of the most confusing features in this field is the variation in units employed by the different manufacturers. No two products on the American market are labeled in identical units. There is a movement to make the standardization of chorionic gonadotropin uniform. This may soon be accomplished. Systematization of unitage in the pituitary or pregnant mare serum extracts is handicapped by the presence of at least two hormones in varying proportions. At present all that can be said is that the unit of Gonadogen (Upjohn) is largest, that of Prephysin (Chappel) and Gonadin (Cutter) are smaller and approximately equivalent, and that of Gonadotropic Hormone (Armour, and Ayerst, McKenna and Harrison) are identical and much smaller than the others. With appropriate doses any one of these materials will accomplish the results to be described in the following illustrative cases.

Clinical Examples—Male Hypogonadism

Interesting examples of sex infantilism are brothers, E. and J. R. (106361 and 106363), ages twenty-four and twenty-seven, who had five siblings normally developed (Fig. 1). The histories and examinations were not remarkable save for high pitched voices, absence of adolescent

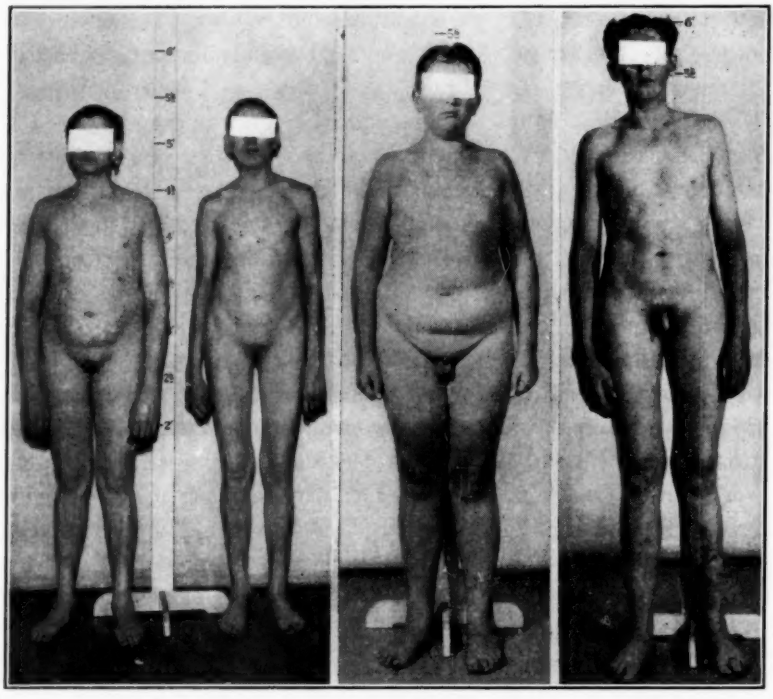

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Brothers with sex infantilism. Fig. 2. Froehlich syndrome, complicated by hypothyroidism. Fig. 3. Eunuchoid, following adolescent testicular atrophy.

interests, absence of beard growth, the distinctly longer span than height, broad type of pelvic girdle, slight obesity in the older one, and the presence in the scrota of small, but firm, testes, with almost no hairs in the escutcheon. Both men have a persistent leukocytosis involving myeloid and lymphoid series, without known reason. Therapy, confined to pituitary gonadotropic extract (Prephysin), 25 units daily for over three months, produced a slight gain in size of testes and penis in each man. For another month the dose was increased to 100 units daily with no further development. The next material used was pregnant mare's serum (Gonadogen), 10 units daily for one month, then 20 units daily for six weeks. Prostatic tissue was just palpable at this stage, but no other progress was evident. After six weeks of daily injection of 250 units of pregnant woman's urine extract (Antuitrin-S) there was no more gain

noted, but after four weeks more of 500 units daily there was a slight tenderness and enlargement of the prostate, slight increase in size of testes, and definite increase in the hair growth of the escutcheon. The older patient began to report frequent erections due to suggestions. A further two months at this same dose level produced no more response than a more wrinkled scrotum, larger but still juvenile penis, and still more frequent erections in both men. At the end of thirteen months both were eager to continue treatment, with the hope of completing their masculine development. It appears that the testicular tissue is probably not capable of much response in these men, for reasons unknown.

Froehlich Syndrome

A much commoner variety of hypogonadism is presented by S. H. (204654), age fourteen, with typical Froehlich syndrome. History was not unusual except that thyroid therapy did not help control the weight or delayed development of genitalia. Physical examination showed no significant findings save those shown in Fig. 2 and the presence of small scrotal testicles. After ten months of daily therapy with pituitary gonadotropic extract (Prephysin), 25 units daily, the penis, testicles, prostate, and pubic hair had all shown gratifying growth. The patient had gained a total of 2 inches in height and the adolescent voice change was in evidence. Blood cholesterol of 230 mgs. per 100 cc. confirmed the diagnosis of hypothyroidism as a complication, and thyroid therapy was resumed, using 2 grains U.S.P. thyroidea sicca daily. This was not until he had demonstrated that on a 1200 calorie diet alone he had lost 22 pounds in four months, during which time he grew one inch taller. Experience here is typical in that weight control depended most upon dietary coöperation; gonad development responded promptly to gonadotropic therapy; thyroid therapy showed results only in its effects on basal metabolism, blood cholesterol, and the character of the skin.

Cryptorchidism

A ten year old boy, W. R. (36115), was seen after he had been given pituitary extract (Prephysin) 1 to 3 times weekly for five months without making the testes descend into the scrotum. He was tall and a bit overweight. The dose was then set at 25 units daily, and after eight weeks a soft mass in the scrotum was believed to be the right testis. The dose was increased to 100 units daily, but numerous doses were missed.

After four months, both testes were about 1 cm. in diameter, but in the canals. A change to pregnancy urine extract (Antuitrin-S), 250 units daily, led to descent into the scrotum in about three weeks. Therapy was continued for four weeks longer, at 250 units twice weekly, after which the testes, now nearly 2 cm. in diameter, remained in the scrotum. During the year of treatment the boy had grown 1.5 inches and had gained 5 pounds. The results certainly suggest that although the pituitary gonadotropic material caused development, the pregnancy urine gonadotrope was more effective in bringing about testicular descent, and also it seems to have stimulated rapid growth in size simultaneously with the attainment of the scrotal position.

Eunuchoidism

A strikingly tall, narrow shouldered and youthful male, E. P. (105-117), was seen when he was twenty-seven, complaining of absence of testes and of secondary sex characters. The atypical skeletal proportions as well as the juvenile penis are shown in Fig. 3. There was no beard, the voice was boyish, the escutcheon was a scanty feminine type, and neither testes nor prostate could be identified. He stated that testicles had been present until the age of seventeen, although small, after which they disappeared without known cause. The use of a month's course of daily injections of pregnancy-urine extract at the age of twenty-three had accomplished no change. He was given daily therapy with pituitary extract (Prephysin) for over three months. The injections were made in the thighs, and led to tender and rounded masses in each inguinal region. When these failed to descend after six months, surgical exploration proved one of them to be a lymph node, and no testicular structure could be found in the inguinal region. There were no subjective changes nor alteration in voice or beard. Thereupon he was transferred to the use of testosterone propionate, which promptly caused increased size of the penis and priapism, indicating that doses smaller than 10 mg. were required. This type of treatment brought about sufficient improvement in an otherwise difficult personality so that the patient and his family were glad to continue its use. Apparently the testicular tissue, if ever present, had atrophied completely.

The obvious difficulties of poor reactivity of testicular tissue in some patients, need for long continued treatment with large doses of gonadotropic material, and uncertainty about the presence of testicles when

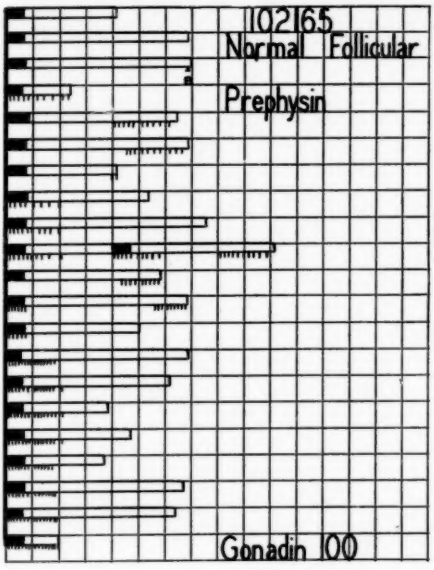

Fig. 4. Infantilism in a female. In all the charts the squares indicate time in weeks, the solid blocks show the duration of menses, the combination of solid blocks and open rectangles indicates the duration of the menstrual interval. B shows the timing of endometrial biopsy, C that of curettage. The small vertical lines under the rectangles indicate hypodermic doses of the gonadotropic extract named on the chart.

they are not palpable in the scrotum have their corresponding difficulties in the female. A further handicap in treatment of the male is the lack of any accepted method by which biopsies may be obtained for study, as from endometrium or vaginal mucosa, and absence of spontaneous and objective cycle of events, like the menstrual flow, by which to judge progress. By comparison it may be seen the diagnosis and treatment of female hypogonadism appears more dependable and with a better prognosis in many cases.

Female Infantilism

As an example of sexual, emotional, and mental infantilism, the progress of M. H. (102165) is gratifying. When first seen at the age of

twenty-one her complaints were of menses at 1 to 3 month intervals, and slight obesity. Members of her family reported behavior suggesting hebephrenic schizophrenia. Intelligence quotient was reported as 0.83 (Binet-Simon). Pelvic examination revealed a small and retroverted uterus. The endometrium obtained on the forty-eighth day was a normally active proliferative tissue but with no evidence of progestational action. Nevertheless, a flow began the following day, which must be classed as anovulatory. Therapy was undertaken with 10 doses of 25 units each, using Prephysin (Chappel) for a series of months as shown in Fig. 4. Simple dietary restrictions were employed, but no other treatment used. Within three months marked psychological improvement was reported by the family. Soon the girl obtained employment, and has continued to support herself for two years, in addition to which she has entered a teacher's college. She earns her way and has done better than average work. Vaginal epithelium studied by smear technique is approaching the normal estrogenic intensity.

Primary Amenorrhea

Partial success in treatment of primary amenorrhea is illustrated by the results achieved with N. S. (94770). She was hospitalized at the age of twenty-five because of personality problems which made her retention in the family home difficult, and employment impossible. Permanent institutional care appeared necessary to the family physician. She refused to allow even a woman physician to make a pelvic examination to determine whether the pelvic organs were present, although the amenorrhea made her fear that she was "turning into a man." The vaginal smear from this case, shown in Fig. 5a, is typical of the castrate type. She was given Prephysin in 100 unit doses daily. The smear showed evidences of estrogenic action within two days, and after 15 doses therapy was interrupted. The vaginal mucosa had changed to the type shown in Fig. 5b. Four days later she experienced her first menstrual flow, which continued for seven days. This sequence proved the presence of ovarian tissue. During almost three years following this time she has received further series of treatments, and has reported a total of four flows. Her mental status improved within the first few months so that her family welcome her presence and help. She has been able to retain employment. She expresses a shy interest in a young man. Studies of the vaginal smear show that some estrogenic activity can be secured when she is given

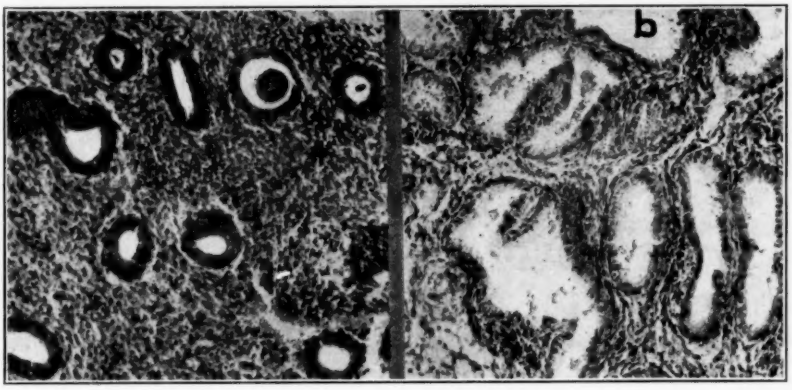

Fig. 5. Primary amenorrhea. (a) Vaginal smear before therapy. (b) Vaginal smear after 10 daily doses of 100 units of Prephysin.

gonadotropic injections, whether this be Prephysin (Chappel), Gonadotropic Extract (Armour or Ayerst, McKenna and Harrison), or Gonadin (Cutter). Omission of therapy for a few weeks on several occasions has led to beginning of a mental relapse. Even though regular menses have not been established, the personality adjustment achieved appears to justify continued therapy.

Less success has followed a similar attempt to stimulate ovaries in G. F. (201240), who was seen at the age of twenty because of primary amenorrhea. The mental and emotional status was normal. Pelvic examination left it uncertain whether there was ovarian tissue. Vaginal smears were of the castrate type, and under stimulation with either pituitary or pregnant-mare serum gonadotropic extracts, there was only occasionally any evidence of estrogenic response. On one occasion a slight flow occurred for three days. It is evident that although this patient had ovarian tissue it was either scanty in amount, or for some reason refractory to treatment with the most potent gonadotropic materials so far available. The prospect of achieving better results by therapy for more than the nine months trial was so poor that the patient was advised to be resigned to amenorrhea with its implied sterility, to which she is satisfactorily adjusted.

Froehlich Syndrome

Typical of the combination of stubborn obesity and genital underactivity is the case of E. M. (86364), who was first seen at the age of

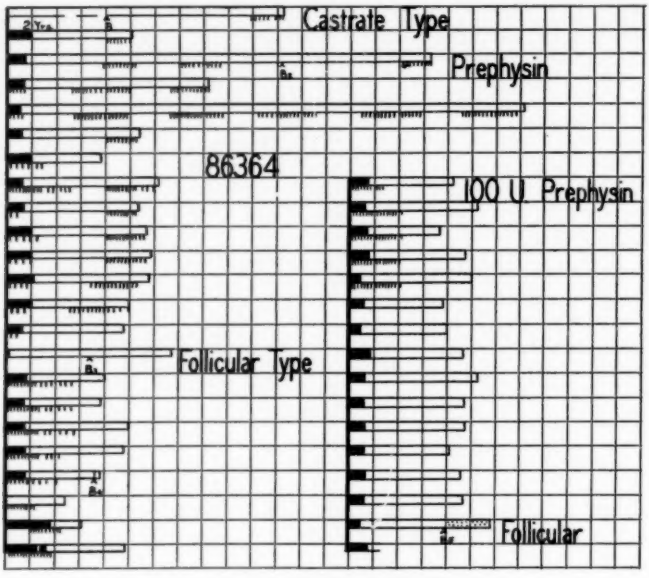

Fig. 6. Froehlich syndrome in a female.

twenty-three. Her menses began at the age of thirteen and occurred at monthly intervals for about eight years, but she had had amenorrhea for the last two years. She had many of the nervous and emotional symptoms of the climacteric type. Although her basal metabolism was above the average, she continued gaining weight with admitted poor coöperation in dietary limitation. Pelvic examination revealed a small and retroverted uterus and a slightly enlarged left ovary. The endometrium was totally inactive. Therapy was continued for thirty-three monthly series, as shown in the chart, Fig. 6. The obvious improvement manifested by return of menstrual cycles led to a series of further endometrial biopsies. Even the latest, taken a year after concluding thirty-six months of treatment, shows less than normal degree of glandular development. No progestational changes have been seen, indicating that these flows are still anovulatory. The vaginal epithelial smears are still a little below optimal estrogenic response. But the nervous and mental symptoms have remained in abeyance, she has coöperated in dieting, and has recently been married. If the period of observation without therapy is marked by return to infrequent menses, it seems worth returning to a further course of gonadotropic injections.

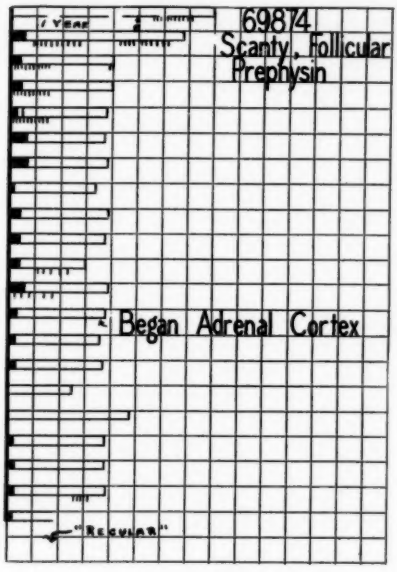

Fig. 7. Secondary amenorrhea, arrested tuberculosis.

Secondary Amenorrhea

Amenorrhea was possibly secondary to pulmonary tuberculosis in B. P. (69874), but by the age of twenty-seven she had had two abortions, spontaneous at the age of eighteen, induced at the age of twenty-six, with obviously low fertility between these events; and a year of amenorrhea after the last abortion. She was asthenic, had a number of complaints of climacteric type, but pelvic examination showed nothing unusual. Endometrium was of low activity, but not castrate in type. The use of gonadotropic therapy (Prephysin) was followed by prompt return to regular cycles, and this gain was maintained without therapy. The regularity of cycles, shown in Fig. 7 is surprising. Because of persistent asthenia, hypotension, and the tuberculous history, a mild Addison's disease was suspected. The use of adrenal cortex extract was symptomatically helpful, although the menses continued about as before, save for a decreased duration of flow. No serious menstrual irregularity has recurred in almost four years since treatment was first undertaken.

Another amenorrheic woman, age, twenty, M. S. (86349), was seen

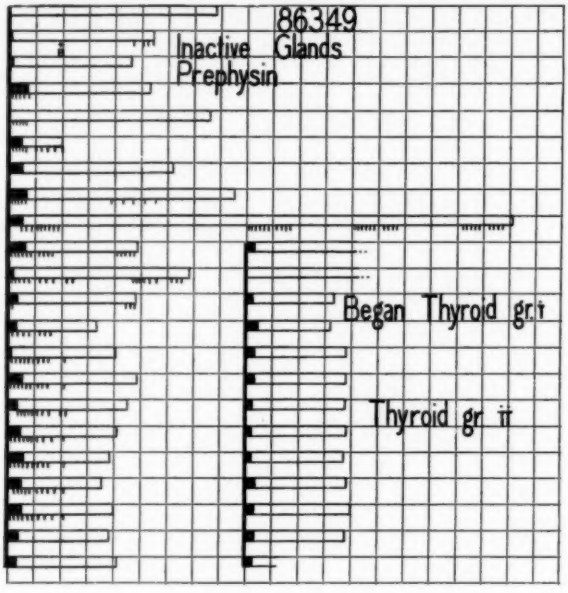

Fig. 8. Secondary amenorrhea, slight hypothyroidism.

after a year without flowing. Except for moderate obesity, a basal metabolic rate of minus 14 per cent, and a small, retroverted uterus, there were no unusual findings. Endometrium was obtainable only with a curette, and showed no more activity than in a castrate woman. Therapy was limited to 25 unit doses of Prephysin, given five and later ten times in the first two weeks of menstrual cycles, or at intervals of at least four weeks when amenorrhea recurred. The chart of her flows, Fig. 8, shows how promptly she returned to more frequent flowing, and how regular monthly rhythm was resumed within fifteen months. Later, after a four month period without therapy, she was started on thyroid alone, due to the persistent slight reduction of the basal rate and the continued obesity in spite of dietary efforts. Menstrual rhythm continues satisfactory, weight control is improved, but there has been no test of the completeness of the ovarian or endometrial cycle of activity.

Infrequent Menstruation

One of the most trying problems in the field under discussion is presented by the emaciated young woman who either will not or cannot

eat an adequate diet, or who cannot maintain a normal weight in spite of an apparently ordinary amount of food intake. Menstrual irregularity of different sorts may appear, but long intervals and scanty flows are common. The term "Simmonds' Cachexia" comes easily to mind, but usually there are not enough evidences of complete pituitary failure to justify such a diagnosis. Typical of this group is a twenty year old girl, V. G. (205784), who had begun menstruating at the age of fifteen. After a few years of four week type of flowing, irregularity appeared, and she was first examined after twelve months of amenorrhea, at which time she had a small and retroverted uterus. Endometrium was not obtainable, even with a curette, and she complained of most of the nervous and emotional difficulties characteristic of the climacteric. She was hypotensive, asthenic, underweight, unable to eat a generous diet, but by studies of salt restriction she was proved not to have adrenal insufficiency. Therapy was a combination of simple suggestive approach to secure a better food intake, and the use of 100 units of anterior pituitary gonadotropic extract (Prephysin) daily for fifteen days, repeated each month. A three day flow appeared just at the end of the first series of such injections, but amenorrhea recurred during the next six months. Therapy had caused little relief from the asthenia and anorexia. At the close of the third series of injections endometrium was obtainable with a biopsy punch, but it showed only a very few tubular glands, dense stroma, and no evidences of mitotic activity in the cells of the glands. A change was made to 100 units of pregnant mare's serum (Gonadin) for the fifteen daily doses, with no greater improvement. It is entirely probable that the substances employed in such cases are useless, not because of low potency, but because they do not supply the materials really needed. Study of the urine of this patient revealed an excretion of gonadotropic hormone which is comparable to that in normally menstruating young women, but without the increased excretion seen uniformly after the menopause has begun. The possibility which needs exploration is that there is deficiency of some other fraction of the pituitary in such cases. So far we can only speculate as to which of the several other pituitary extracts might be helpful for such a woman with the combination of amenorrhea, anorexia, asthenia, climacteric nervous symptoms, but without the usual climacteric exaggeration of gonadotropic excretion.

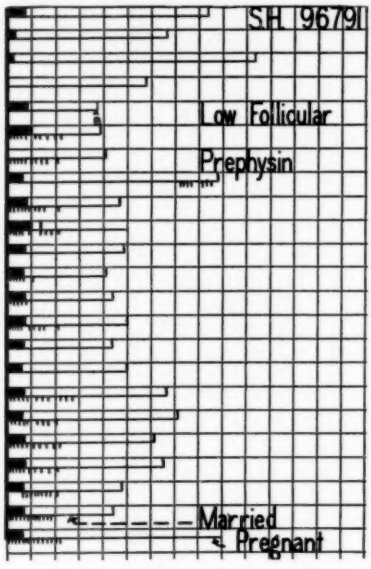

Fig. 9. Irregular menstruation with infantilism.

Irregular Menstruation

As an example of irregular and slightly infrequent menstruation, the record of S. R. (S. H. 96791) under therapy is encouraging. She was first seen at the age of nineteen, with a history of six years of totally irregular intervals, varying from one to ten months, usually about two months, with flows decreasing from seven to three days in duration, and with no help from the use of pregnant woman's urine concentrate or estriol. There were no nervous symptoms. Pelvic examination showed the familiar small and retroverted uterus. A biopsy showed loosely organized endometrium containing a few tubular glands, with very little mitotic activity, in spite of a twenty-five day interval since the last flow. The following day anovulatory bleeding of seven days began. The record of cycles is shown in Fig. 9 where improvement following therapy is evident. The doses were limited to 25 units of Prephysin ten times in the first two weeks of each cycle. After a little less than a year therapy was omitted, and two months later menstrual intervals began to lengthen. The vaginal epithelial smears showed almost no estrogenic activity. Therapy was resumed, and the epithelium showed progressive

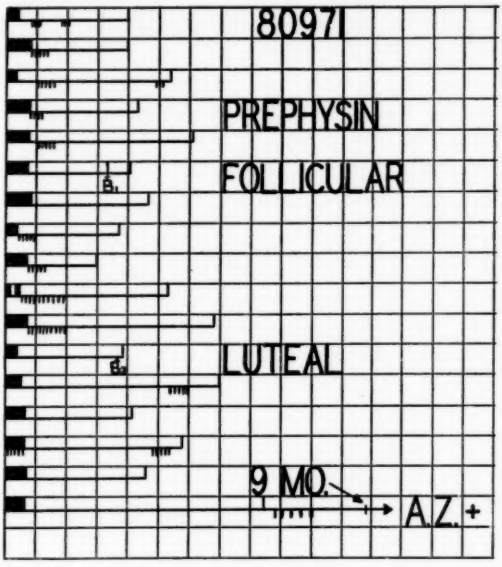

Fig. 10. Anovulatory flowing with sterility.

improvement to nearly a normal intensity in two cycles. After eight months she was married, and had only one flow before becoming pregnant due to carelessness about contraceptive practice. Results are not always so easily attained.

Anovulatory Flowing

Another case record has some similarities to the last one described. This twenty year old student, L. H. (80971), had likewise flowed very irregularly from the age of sixteen, previous to which flows had occurred at about six week intervals. Uterus was small. The chart of her cycles in Fig. 10 shows little progress in improving the rhythm. After several months of treatment with pregnant woman's urine concentrate the use of Prephysin was begun. Following six months of this an endometrial biopsy in the fourth week showed a fairly active follicular hormone effect (Fig. 11a), but the flow which followed within seven days was probably anovulatory—certainly not preceded by a normally active corpus luteum. Therefore, therapy was resumed and after six months a second biopsy showed a well matured progestational endometrium (Fig. 11b). During the previous two years of married life this patient had

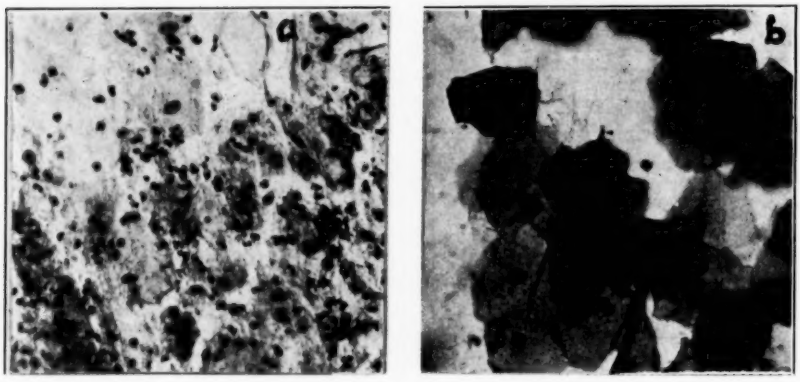

Fig. 11. Relief from anovulatory flowing by continued treatment. (a) Proliferative endometrium in the fourth week, hypofunction. (b) Progestational endometrium in the fourth week, normal function.

become careless of contraceptive technique, for she knew of her underactive ovarian problem. Although she was told that the progress she had made under therapy was toward improved fertility, the irregularity of menses continued, and she was surprised to find herself pregnant. Her baby was born at term with an uneventful pregnancy. During the ensuing two years, with no endocrine therapy, she menstruated at four to five week intervals.

Menorrhagia

A slight variation from this type of disturbance is presented by K. M. (91934), who was referred for examination at the age of twenty-nine because of repeated menorrhagia, with intervals essentially of a four week type, but duration of flow from three days to two weeks. She had repeated basal metabolic rates of 23 per cent or more above normal, but too few physical findings to justify a diagnosis of thyrotoxicosis. Thyroid therapy seemed contraindicated. Trials of pregnant woman's urine and of corpus luteum extracts had been of no avail. It is probable that mumps a year earlier had some etiologic importance. Pelvic examination showed an enlarged and retroverted uterus, from which the curette produced tissue with enlarged glands of varying sizes characteristic of the "Swiss cheese" endometrium. The uterus was replaced and supported by a pessary, but the menorrhagia recurred, as shown in Fig. 12. Thereupon she was treated with pituitary gonadotropic extract (experimental

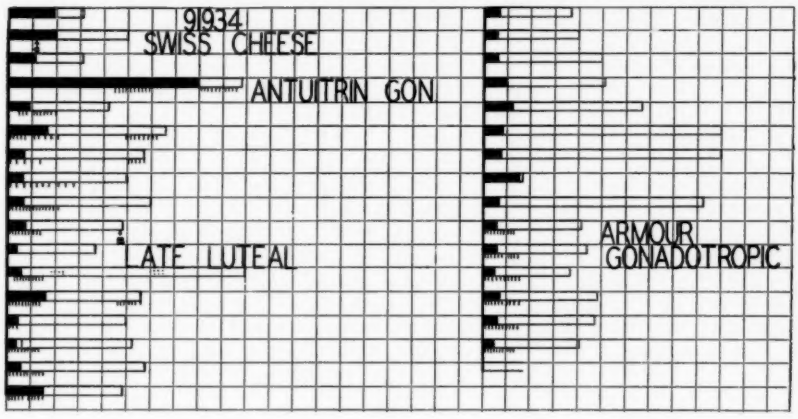

Fig. 12. Menorrhagia, relieved by use of gonadotropic therapy

material from Parke, Davis and Company) with definite improvement, which became evident after a few months. One year after the first examination a biopsy produced endometrium with typical progestational endometrium, demonstrating the normal and complete ovarian cycle. After six more cycles of treatment, the pituitary extract was omitted, but the intermenstrual intervals gradually lengthened, and the menorrhagia returned. When therapy was resumed with a stronger preparation, the Gonadotropic Pituitary Extract (Armour), there was immediate return to regularity. Such results have convinced us that menorrhagia is to be considered as hypofunction of the ovaries if it is due to any endocrine anomaly.

Sterility

Although it is apparent that many of the types already presented were, or probably would be sterile, there are some instructive features in the record of S. N. (74900), a thirty-three year old mother of a two year old child, who was disappointed because of her inability to conceive again. After the pregnancy she had noted menses as infrequently as three months, and dysmenorrhea had occurred for many days. Obesity, acne, and many of the climacteric complaints had appeared. The basal metabolic rate was above normal. Pelvic examination revealed a retroverted uterus which was held in place with a pessary. The ovaries were enlarged and cystic. Endometrium obtained at the end of the fourth week showed only a low intensity of estrogenic effect. Flow did not appear

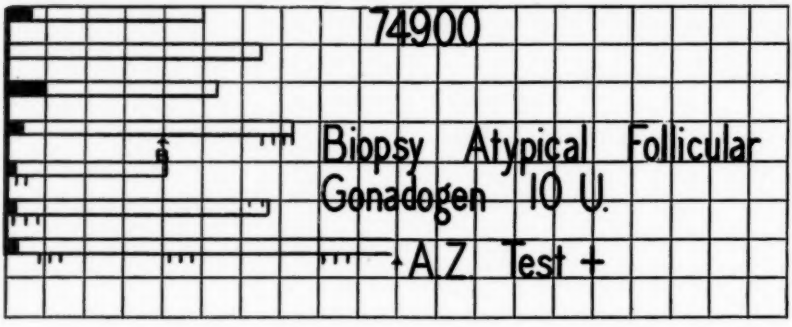

Fig. 13. Postpartum sterility, relieved by gonadotropic therapy.

until more than three weeks later, so that it is impossible to determine whether ovulation ocurred in that cycle. Therapy was begun, using pregnant mare's serum concentrate (Gonadogen), 10 unit doses as shown in Fig. 13. After only twelve doses, in four cycles, a longer amenorrhea than usual was marked with nausea, and the urine test indicated pregnancy, which went to term. She was given progesterone, without any known need, to reduce the risk of abortion. Pregnancy following such brief treatment is surprising. Such occurrences have been repeated, and serve to indicate that in some women a relatively small amount of pituitary treatment is sufficient to restore a fertile ovarian cycle.

Repeated Abortion

Typical case reports of treatment of repeated abortion will not be presented, for they are being separately published by my colleague in this field of investigation, Doctor Ralph E. Campbell.[24] In his series there are thirteen women who have aborted two or more times previously, of which number eleven have now delivered living children at term. The treatment has been based on the use of progesterone, employing preparations made at the University of Wisconsin, and commercial material such as Proluton (Schering) and Progestin (Upjohn). The doses have been 1 to 3 units three times weekly, the maximum dose 5 units, and the duration of treatment usually lasting into the fifth month.

We have no data on the relative merits of progesterone and of chorionic gonadotropic extract. Theoretically the material from the urine of pregnant women should maintain the activity of the gravid woman's

corpus luteum and accomplish the same results. Comparative results are not yet available in the literature.

Premature Climacteric

It is admittedly impossible at this time to draw a sharp line between the cases of secondary amenorrhea and other varieties of ovarian failure above described, and those which can be listed as premature climacteric. Attention may be directed to a rather striking type of history illustrated by the case of H.H. (204902), age twenty-four, who had a child born when she was nineteen, after which menstrual irregularity became evident and led to amenorrhea at age twenty-three. In addition to several typical climacteric complaints she noted almost constant breast pain, and she was asthenic and hypotensive, but ate normal amounts of food. The uterus was found to be distinctly small, the endometrium totally inactive, and the vaginal mucosa was atrophic, resembling that in the castrate. The use of 100 units of pituitary gonadotropic extract (Prephysin) daily for ten doses, repeated at four week intervals, led to a minimal estrogenic response in the vaginal mucosa, but no flow ever appeared. It was, therefore, concluded that the only effective therapy was symptomatic relief of climacteric symptoms by the use of estrogenic substances. The use of estrogens for this purpose will be described in a subsequent paper by Doctor Ephraim Shorr,[14] and will, therefore, not be further discussed.

Dysmenorrhea

Although the relief of menstrual pain is one of the gynecologist's commonest problems, we confess to no dependable means for relieving this type of discomfort. The fundamental causes are still unidentified. We can be certain that pain may attend either flows preceded by corpus luteum formation or those which are anovulatory. One encouraging observation is typified by the results of treatment of E. B. (94088), a student who was referred at the age of eighteen because of pain, but who flowed at variable intervals of one to nine months. There were no other findings to suggest incomplete development. Endometrium showed progestational changes well developed early in the fourth week. Since the flows occurred so infrequently, she was treated with 100 unit doses of Prephysin ten times in the first two weeks of each cycle. A striking improvement in rhythm occurred, with intervals averaging five weeks,

and the patient had satisfactory relief from pain. Omission of the therapy for more than two cycles was followed by return of the pain. We cannot draw far reaching conclusions from such observations, but we have observed such improvement at times in treating underdeveloped girls. On the other hand, the majority of such patients do not have any serious pain. The mechanism by which pain was relieved may be similar to that involved in relief of dysmenorrhea by estrogens. Again estrogens have been known to exaggerate dysmenorrhea. From the endocrine point of view dysmenorrhea is still a fertile field for exploration. A recent report from two of my colleagues[25] demonstrates the help which may be obtained by the use of thyroid. If time permitted, I might cite examples of relief from dysmenorrhea, menorrhagia, irregular menstruation, premenstrual tension states, and other menstrual disorders by thyroid. This type of therapy has been depended upon in cases where the basal metabolic rate, blood cholesterol, and the physical findings made relative hypothyroidism the probable diagnosis. The importance of thyroid disorders must not be lost sight of in our study of the direct relationships of anterior pituitary and ovaries. There are other endocrine and somatic problems which challenge the breadth of view of the diagnostician. But the types of results presented here lead us to the following conclusions:

Conclusions

1. The chief disorders of gonadal endocrine function are to be classified as hypofunction of the gonad, either primary or secondary to that of the anterior pituitary.

2. Gonadal hypofunction may be a consequence of disturbance in thyroid secretion, of other endocrine disorders, or of various systemic diseases.

3. Disorders of gonadotropic secretion by the anterior pituitary are especially frequent in the following circumstances: during the rapidly changing period of adolescence, during and immediately after pregnancy, and at the climacteric, either spontaneous or induced.

4. The frequent association of obesity with menstrual disorders is still unexplained, but it seems probable that the obesity is more a result of disturbances in the hypothalamic region than of the hypofunction of either pituitary or gonads *per se*.

5. For accurate diagnoses of the types of menstrual disorder and for estimating progress under treatment, the use of properly timed endo-

metrial biopsies, smears of vaginal mucosa, and determinations of urinary pregnandiol output are invaluable. Only the first two are generally available.

6. Assays of hormone content of blood and urine are still used only as research tools.

7. Estrogenic substances are useful chiefly for relief from climacteric symptoms, or from gonorrheal vaginitis in young girls.

8. Progesterone is helpful so far only in preventing repeated abortion.

9. Among gonadotropic materials the chorionic product is helpful in stimulating growth of testes and descent of some cryptorchid organs. It does not stimulate the human ovaries. Anterior pituitary extracts or concentrates from the serum of pregnant mares will accomplish stimulation of testes or ovaries in the human.

10. The optimal therapeutic program with pituitary gonadotropic extracts in the male is based on daily injection of small to moderate doses.

11. Optimal results with females are secured by use of cycles of injections. To stimulate the follicle the doses should be confined to the first two weeks of the menstrual cycle. To initiate ovulation the gonadotropic extract needs to be given intravenously. It is probable that sustained luteal secretion can best be stimulated by hypodermic therapy after ovulation.

12. Favorable results have been reported following the use of Prephysin (Chappel), Gonadogen (Upjohn), Gonadin (Cutter), and Gonadotropic Extract (Armour or Ayerst, McKenna and Harrison). The units of these materials are not interchangeable.

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PUBERTY, MENSTRUATION, PREGNANCY*

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My mandate covers three critical periods in the life of woman: puberty, menstruation and pregnancy—more than four decades of her existence. Because many of the terms and concepts used in endocrinology are not clearly understood by all members of the profession, I shall give definitions of some of the terms employed.

GONADOTROPIC FACTORS stimulate both the male and female gonads. In this connection the tests used in the female animal are described. In response to gonadotropic factors the ovarian follicles and corpus luteum in the ovaries of immature animals are activated. There is a difference between the factors obtained from the prepituitary glands and those derived from pregnant mares' serum, which act upon the ovaries of hypophysectomized animals, and extracts of pregnancy urine and placenta which act mainly upon intact animals. The former (gland extracts) should be called *gonadotropic factor,* the latter (pregnancy derivatives), *chorionic gonadotropin.*

FEMALE SEX HORMONES include both estrogens and progestin. *Estrogens* are hormones mainly secreted by the ovarian follicles, corpus luteum and placenta. They produce estrus in the castrate rodent (mice, rats, rabbits, etc.).

Progestin is the special corpus luteum hormone which causes secretion and a decidual reaction in the uterine mucosa. Without these preparatory changes the fertilized ovum cannot embed.

ANDROGENS are the male sex hormones which produce comb growth in capons and immature chicks of both sexes, and restore the atrophic prostate and seminal vesicles of castrate animals. In addition to derivation from the testes, androgens have been obtained from the adrenal.

As in this series of talks no emphasis has been placed upon the intrauterine, childhood and adolescent periods, in passing I must mention that within the uterus of the mother, throughout nine months, the

* Read November 3, 1939 at The New York Academy of Medicine in the Twelfth Graduate Fortnight.

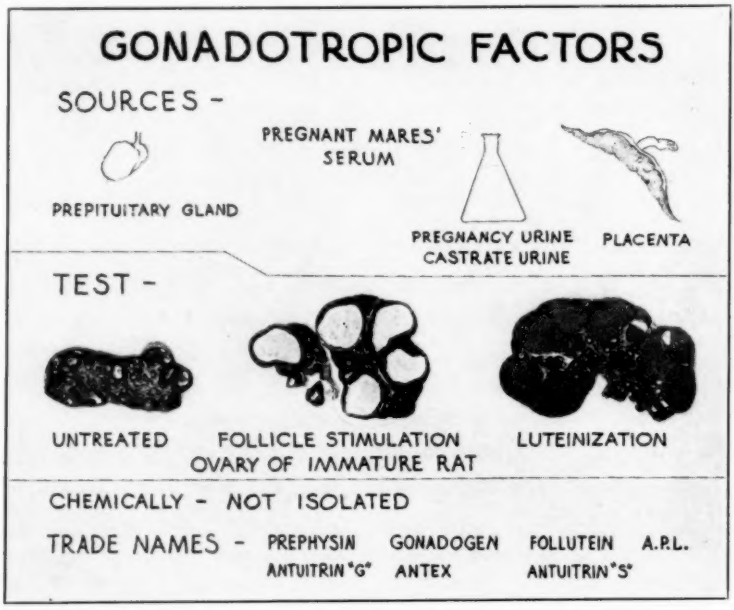

Fig. 1. Gonadotropic Factors. Gland extracts; concentrates of pregnant mares' serum; concentrates of pregnant human urine, and of placental tissue are available.

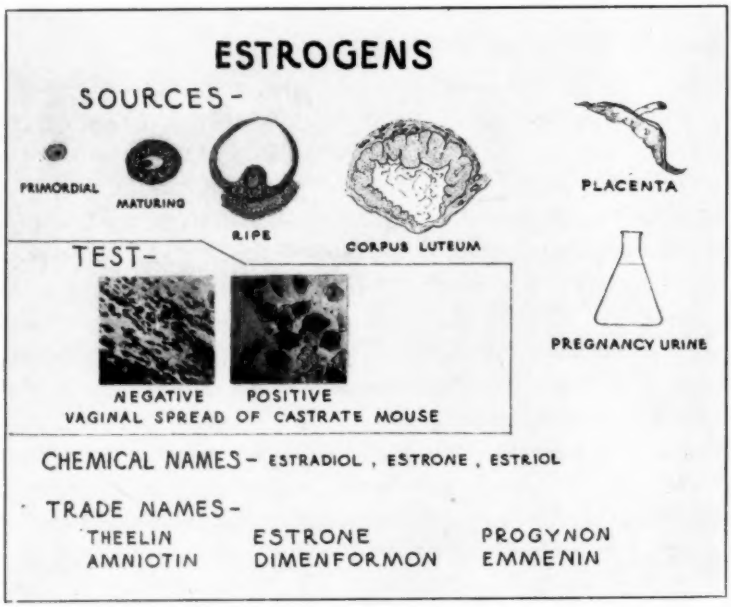

Fig. 2. Estrogens. Main source stallions' urine; other, from placenta.

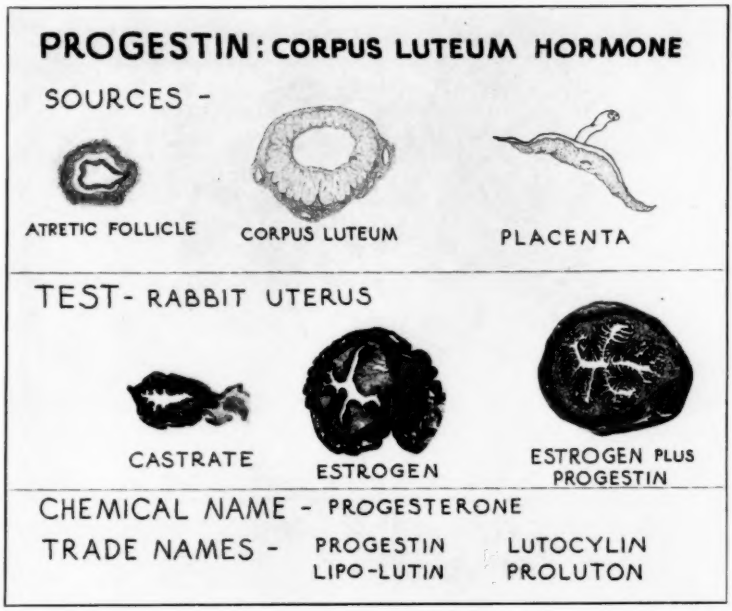

Fig. 3. Progestin. Made synthetically. Cross sections of uterus from E. Fels. *Das Hormon des Corpus Luteum.*

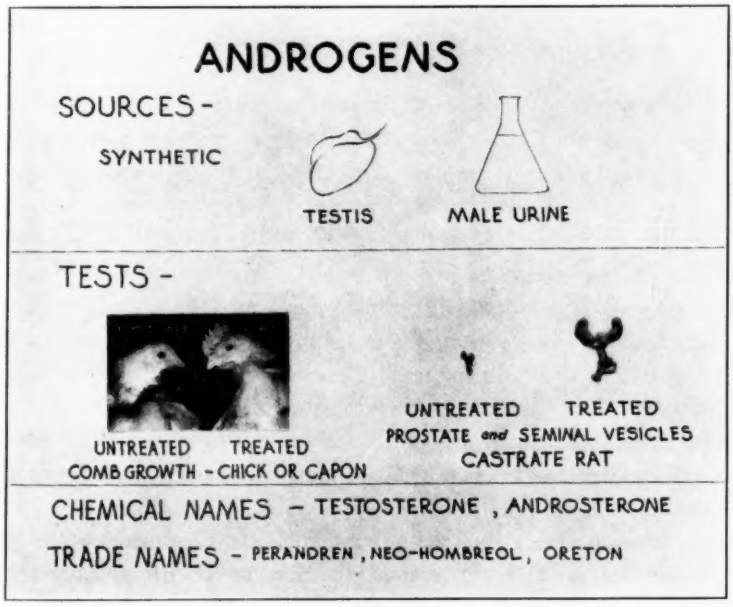

Fig. 4. Androgens. Made synthetically.

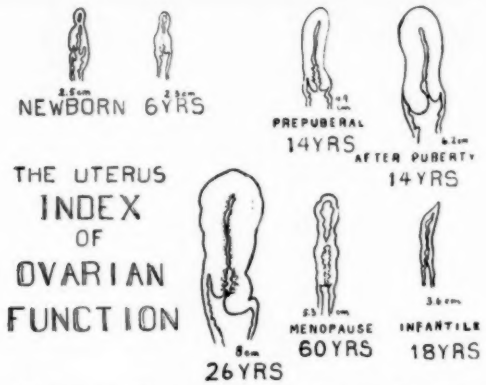

Fig. 5. Cross Sections of Human Uterus at Various Ages. Drawn to scale. Some are redrawn from H. Bayer, *Vorlesung über allgemeine Geburtshilfe.*

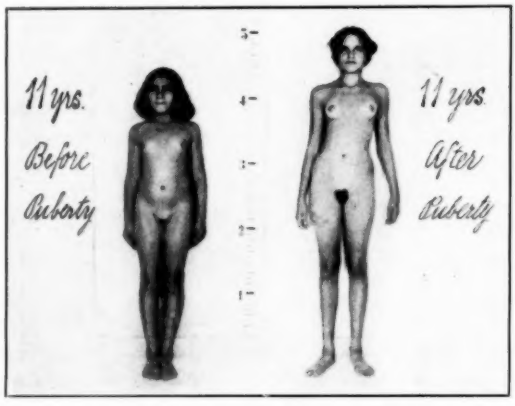

Fig. 6. Puberty Changes. At left, girl before puberty; at right, another girl of same age who menstruates.

sex organs of the fetus are stimulated by maternal and placental hormones, reaching them through the placental circulation. Therefore, at birth the uterus and breasts by their comparatively large size show anatomically the effects of this hormonal stimulation—the well known symptoms of activation, popularly known as pseudomenstruation and witch's milk. In the ensuing years the tubular organs of the female infant are smaller than at birth, but gradually by the time that the fifth year is reached, a slowly progressive increase in size of the ovaries and

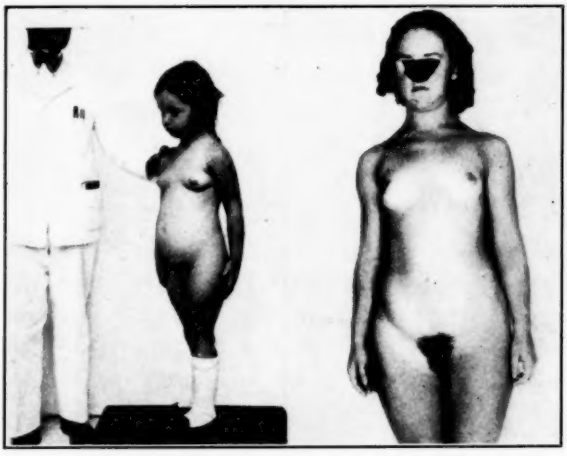

Fig. 7. Pubertas Precox. At left, child of 3 years who menstruates since age of 6 months. At right, same child at 11 years now a normal adolescent.

uterus can be noted. In the infant and adolescent, small quantities of female sex hormone, as well as male sex hormone, are excreted in the urine. In a girl, accidentally investigated three months before the onset of her menstruation, a definite sex cycle in the urine could be demonstrated.

Puberty

Puberty is not an instantaneous, but a slow, progressive process. Clinically it manifests itself by the development of pubic and axillary hair, increase in size of the breasts, changes in the fat distribution, which becomes more markedly feminine, slowing or arrest of growth, and a very definite psychical and emotional transformation toward the feminine. The most obvious evidence of the full development of normal puberty is the onset of menstruation. However, absence of menstruation, that is true primary amenorrhea, may mask the exact determination of the time of puberty.

The hormonal forces which produce puberty have been discussed by previous speakers. Nevertheless, no convincing explanation, for the onset of cyclical pituitary function which initiates the ovarian stimulus has as yet been adduced. The activated ovary produces the follicular and luteinizing phases in the uterus and the complete cycle terminates in menstruation.

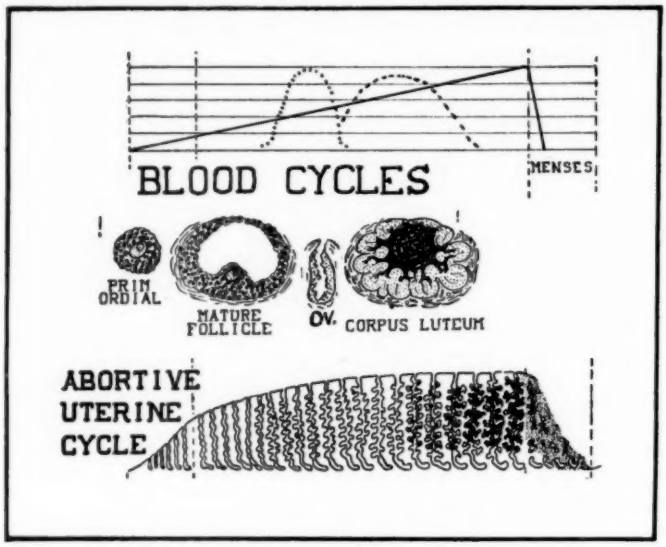

Fig. 8. Diagram of Blood, Ovarian and Uterine Menstrual Cycles. *Above: Blood Cycle:* Solid line, estrogens; dotted line, prepituitary; broken line, progestin. *Middle:* Follicle, ovulation (Ov.), corpus luteum. *Below:* Uterine mucosa.

Puberty is largely dependent upon normal infantile and preadolescent development. However, the menarche may occur in very badly handicapped individuals, and fail to appear in adolescents who show few or no recognizable endocrine disturbances. The most common and most easily diagnosed as well as remediable postponements of puberty are due to hypothyroidism, obesity or severe malnutrition. It is my firm conviction that many of the disabilities noted in the female genital tract in adults might have been avoided if we had had the opportunity of recognizing these disturbances during adolescence and the ability to remedy them at this stage.

The time of onset of puberty and menstruation varies greatly, influenced by individual, familial, ethnic and climatic factors. Premature sexual maturity (noted as early as three months) may be due to unknown causes (so-called essential), or to tumors of the ovary, pineal or adrenal glands.

Menstruation

Menstruation marks the stage of maturity in the female. The men-

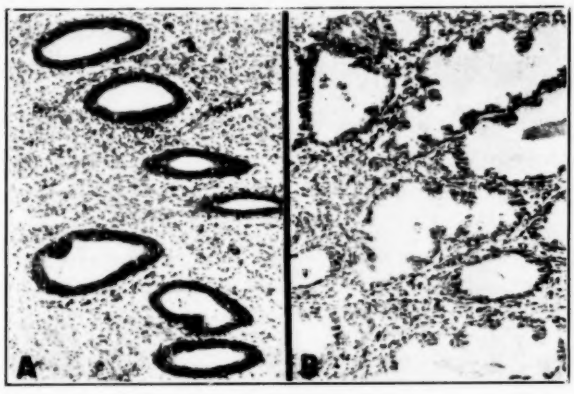

Fig. 9. Low Power Photomicrograms of Uterine Mucosa. A. Proliferative stage. B. Secretory stage.

strual cycle should begin with the onset of puberty, persist throughout the time of sexual life, and gradually fade with the approach of the menopause. The sole physiological interruptions of the menstrual cycle are caused by pregnancy and lactation.

In the normal adult female—

1. Periodic increased gonadotropic action of the anterior pituitary activates the ovaries, which respond with

2. Follicle growth, maturation of the follicle and ovulation.

3. The ovarian follicles produce *estrogen* and, after ovulation, the empty follicle sac forms the corpus luteum. This in turn secretes *progesterone* in addition to estrogen.

These two hormones (estrogens from the first to the thirteenth day; estrogen and progesterone from the thirteenth to twenty-third day) by means of the blood stream reach the uterus, tubes, vagina and breasts which are the end organs upon which these secretions act.

The biologic purpose of the uterine changes which ensue has for its sole object the preparation of a nest for a fertilized ovum. The changes in the endometrium are divisible into the estrogenic (follicular) and progestational (corpus luteum) phases, both characterized by distinctive and, if well marked, readily recognizable histologic pictures, respectively, proliferation and secretion.

If fertilization does not occur, the ovarian stimuli cease, involutional intrauterine changes abruptly supervene, culminating in the endometrial

desquamation or transmucosal bleeding which we term menstruation. Physiologically menstruation in the human may be regarded as a pseudo-abortion.

These monthly processes have been thoroughly studied from many angles, including the morphologic changes which have been observed in the hypophysis; the full sequence of growth of the primordial follicle to the Graafian stage; its rupture and corpus luteum formation in the ovary; the hormonal cycles (gonadotropic, estrogenic, proluteinic) in the blood and urine; and the consequent changes appearing in the end organs.

Variations in the twenty-eight day menstrual cycle are frequent. They commonly take either the form of diminution, retardation or omission of menstruation, or their *clinical* antithesis, namely, increased amount, prolongation or too frequent flow.

Amenorrhea, however, may occur in the presence of apparently adequate hormonal blood cycles.

Menorrhagia and metrorrhagia most frequently are due to overfunction of follicular ovarian action. Some but as yet indecisive evidence has been offered that particular types of excess bleeding are due to quantitative disturbance between follicular and lutein phases. I shall again refer to this subject.

Pregnancy

Somewhere in the lifetime of a female, impregnation may occur; this happens most often around the eleventh to fourteenth day of the cycle. If then the fertilized ovum reaches the progestational endometrium, it should embed and grow there. From the very onset of nidation, a tremendous change in the hormonal balance ensues. The anterior pituitary-like hormone found in the blood and in the urine increases a thousand-fold over that found in the non-pregnant. Upon this change are based the pregnancy tests (Aschheim-Zondek; Friedman). The amount of estrogen progressively increases both in the blood and in the excretions, from the second month onward. A steadily progressive increase in the urinary progesterone has likewise been noted until the fifth month.

Such tremendous acceleration of hormonal stimuli manifests itself by striking general changes: increase in size of the uterus, development of the breasts, increased vascularization of the genital sphere, and the speeding up of many endocrine functions (pituitary, adrenal, thyroid). The

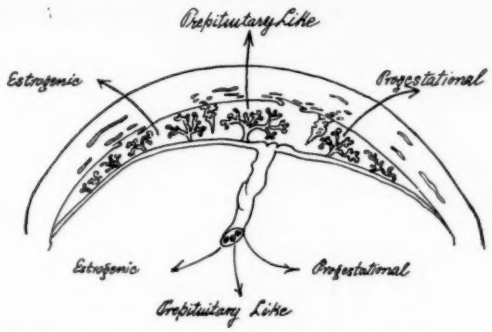

Fig. 10. Diagram of Placental Secretion. "The Gestational Gland." *Upward* pointing arrows show secretion into maternal circulation, *downward,* into fetal blood stream.

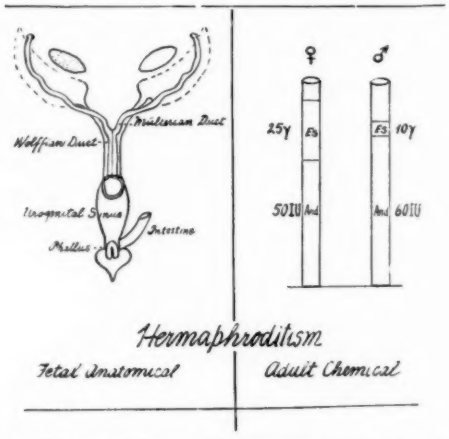

Fig. 11. Diagram of "Normal Human Hermaphroditism. *Left.* Early fetal bisexual development of Wolffian and Müllerian ducts. *Right.* Chemical adult hermaphroditism. Presence of estrogens and androgens in blood and excretion of both sexes.

placenta develops into a temporary gland of internal secretion (the Gestational Gland) which produces locally anterior pituitary-like (chorionic gonadotropin), estrogenic and progestational hormones, affording to the uterus and its contained fetus an almost autonomous supply of sex hormones.

In spite of much investigation, a hormonal causation of labor has not as yet been firmly established. With the expulsion of the fetus and placenta, a rapid return to the pregravid status, in fact a slump below the

normal production of hormones, takes place, causing hyperinvolutionary changes when exaggerated or prolonged.

Ratio of Femaleness to Maleness

Recently an additional factor has had to be considered. After the discovery of an adult chemical hermaphroditism in both sexes, which shows itself by the presence in the female of male sex hormone and in the male of female sex hormone, the ratio between maleness and femaleness in a given individual has assumed importance. Which of the malfunctions or functional diseases can be ascribed to severe disturbances of this ratio, femaleness to maleness, is still a moot question which is being investigated in numerous research laboratories. A striking example is observed in the female in the adrenocortical syndrome.

Functional Disturbances

The foregoing briefly and in bare outline covers the essentials, as far as known, of the complicated hormonal processes which produce puberty and control menstruation, as well as pregnancy. Deviations ascribable to hormonal changes are known as functional diseases. Of these functional disturbances, I instance a few clearcut clinical entities, though I must warn you that, upon analysis, their hormonal basis is still little understood. In the first group fall mainly the amenorrheas, both primary and secondary, sterility and dysmenorrhea; in the second, menorrhagia, metrorrhagia and premenstrual tension.

Before ascribing these symptoms to functional disturbances, it is essential that we exclude organic diseases. In the amenorrhea group, such conditions as malformations of the genitals (absent vagina) and pregnancy frequently have been overlooked. In the second group, of excessive bleeding, fibroids and neoplasms, particularly of the ovaries and of the cavity of the uterus, are the most frequent causes of error.

In order to obtain an insight concerning the hormonal conditions met with, our group has sought to devise methods of concentration for estrogens, androgens and gonadotropic factors obtained both from the blood and the urine.

Unfortunately the blood concentration of hormones normally is low and therefore only one animal may be used for each test unless unjustifiably large amounts of blood are withdrawn. Some physiologists have therefore taken exception to these results because, as is well known, the

reactivity of individual animals varies greatly. Fully aware of this variability, we have graded our blood tests considerably above the average reactivity of the animal used. For example, before menstruation, 30 cc. of normal woman's blood should contain a mouse unit of estrogen; we use 40 cc. This allows a wide margin. Fourteen years trial has convinced us of the reliability of the estrogenic and gonadotropic blood tests. If more delicate tests become available, they may alter the number of units obtained, but probably will merely change the scale without affecting their relative proportion. The urine tests are performed with larger groups of animals and the results therefore meet statistical requirements.

Our further investigations have necessitated a revision of the view, first entertained, that amenorrheas are always due to underfunction of the ovary. It appears that no single cause can be found for amenorrhea. Amenorrheic women may secrete a normal amount of estrogen, too little or even too much. The gonadotropic cycle in both blood and urine may likewise be normal, high or low.

These findings in amenorrhea are difficult to interpret, particularly as we have also found that amenorrheic women, in contrast to women in the full menopause (women even up to seventy years), *require from six to ten times larger doses of estrogen than in the menopause*, to produce a single uterine bleeding. This may signify that the uterus in amenorrhea is more refractory to estrogens.

The hormone titers obtained in functional sterility closely parallel those obtained in amenorrhea, that is, normal, under, or overfunctioning of the ovaries. Recently we have seen that amenorrheic as well as sterile women may have what is considered a normal excretion of sodium pregnandiol in the urine. If the interpretations of Venning and Browne are accepted, this would signify ovulation. I am as yet unwilling to accept the presence of sodium pregnandiol in the urine as conclusive evidence of ovulation. It must not be forgotten that in the growing and atretic follicles, the thecal tissues frequently show luteal proliferation, which may well account for a progestational excretory product. This does not signify that I agree with some clinical investigators that the anovulatory cycle is as common in the human being as has been suggested.

In menorrhagia and metrorrhagia the blood concentration of gonadotropic and estrogenic hormone may be normal; more often it is low. The urine excretion of estrogen, on the other hand, is regularly excessive, a characteristic of this group. Instead of the normal excretion of

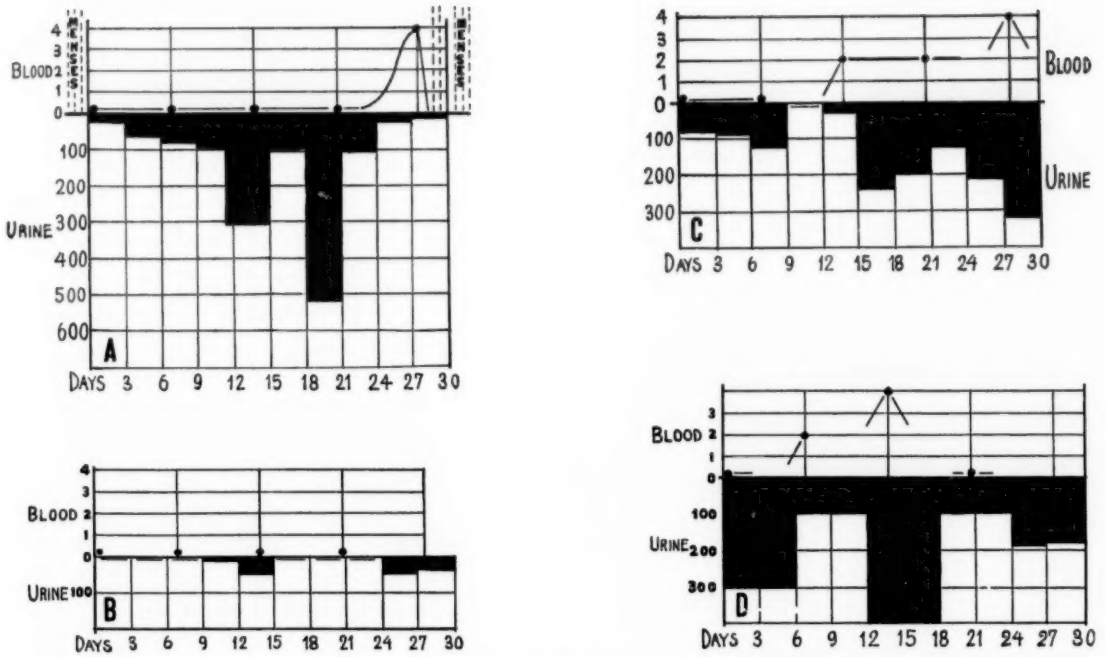

Fig. 12. Graphs of Estrogenic Blood and Urinary Cycles. A. *Normal Menstruating Female.* Premenstrual blood concentration corresponding to 25 M.U. per liter. Total excretion in urine in 30 days equals 1500 I.U. B. *Primary Amenorrhea.* Acyclical. No demonstrable blood concentration. Total excretion 135 I.U. C. *Secondary Amenorrhea.* Four years' duration. Cyclical blood concentration; normal excretion (1400 I.U.). D. *Primary Amenorrhea.* Cyclical blood concentration. Excretion somewhat above normal (2200 I.U.).

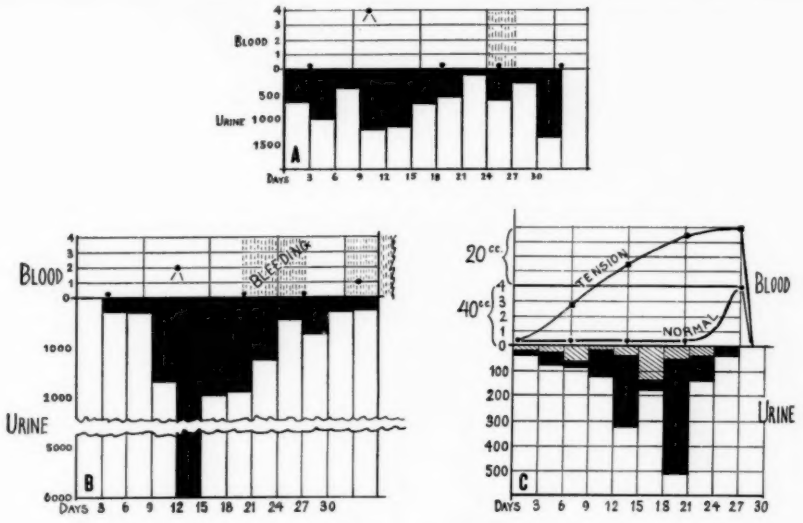

Fig. 13. Graphs of Estrogenic Blood and Urinary Cycles. A. *Menorrhagia.* Cyclical blood concentration. Excretion 7500 I.U. B. *Menorrhagia.* Subthreshold blood concentration; excessive urinary excretion (15,000 I.U.). C. *Premenstrual Tension.* Contrasting normal and "tension" premenstrual blood concentration. Urinary excretion in "tension" 400 I.U. (shaded), in contrast to normal, 1490 I.U. (solid black).

1200 to 1500 international units of estrogen, from 2500 to 15,000 units are excreted during this same period of time. These findings may be interpreted either as ovarian overproduction or failure of utilization of estrogenic hormone.

In contrast, in a group which I call "premenstrual tension," characterized by excessive neurovascular and psychic phenomena preceding menstruation, at once relieved by the appearance of the menstrual flow, different hormonal findings are observed. The blood concentration of estrogen is increased throughout the cycle. Premenstrually a positive reaction is regularly obtained with 20 cc. of blood instead of 40 cc. The urinary excretion is greatly diminished, only from 300 to 500 international units of estrogens being excreted during thirty days. According to my present interpretation, this signifies a retention of estrogens in the blood stream, with resulting autonomic symptoms.

Whether variations in kidney permeability (either too high or too low threshold) with consequent differences in blood hormone levels,

irrespective of ovarian activity, or non-utilization and failure of destruction of the estrogens play the decisive role, must remain an open question.

Therapy

To the patient, as well as to the physician, successful therapy is of vital importance. The results obtained by means of the various hormones have always given rise to the utmost diversity of opinion. The practitioner is in the unfortunate position of having to depend largely upon the reports of laboratory and clinical investigators. Animal experimentation allows of various interpretations. Clinical investigations, unless striking, as in the present treatment of the menopause, are almost impossible to evaluate critically.

Some of the effects of estrogens, such as the conversion of the thin, non-resistant vaginal epithelium of the infant into a thicker keratinized mucosa, are well authenticated and are of help in the cure of infantile and adolescent gonorrhea. The relief of menopause symptoms by means of the natural and synthetic estrogens is well established. Progesterone appears promising in the treatment of dysmenorrhea and habitual abortion, although the effects are not as clearcut. Even less assured, though still promising, is the reduction of bleeding in functional menorrhagia and metrorrhagia by means of progesterone. The treatment of excessive functional bleeding with androgens theoretically meets many requirements because its primary effect in reducing the gonadotropic excretion of the pituitary is what is sought for, and little if any stimulation of the uterus results. Androgens at times, however, have produced masculinizing symptoms such as hirsutism, coarsening of the voice and increase in size of the clitoris, only the latter appearing reversible. Therefore I counsel against the use of male hormone in the female unless possibly vital indications necessitate its employment. In my hands estrogens as well as gonadotropic prepituitary preparations have proved of no value whatever in the treatment of amenorrhea.

In spite of many glowing reports, I am unable to record any results obtained in the female with prepituitary gonadotropic factors, whether obtained from the gland or concentrates of pregnancy urine, with the possible exception of some increase in the growth of pubic hair.

I am entirely unconvinced by the evidence submitted that the available prepituitary gland preparations, whether labeled "growth" or "gon-

adotropic" have any therapeutic effect on body growth or on the female genital function. For every case reported as cured by daily injections, given over periods of twelve to thirty-six months, I can show a greater number of patients in whom two to five inches of growth has taken place unexpectedly in the course of one to three years (hypogonad; pseudo-Froehlich) and others who have menstruated for the first time, or after periods of amenorrhea of two to seven years duration, without any therapy. The intravenous injection of concentrates of pregnant mares' serum may prove more effective.

In regard to prepituitary therapy, therefore, we still are in the dark epoch comparable to that of thirty years ago when the profession, at large, dosed their patients with inert, defatted ovarian powder and reported good results which then, as now, should be credited to Mother Nature.

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THE PHYSIOLOGY AND PSYCHOLOGY OF CONVALESCENCE*

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THE word, convalescence, is used by us today exactly as it was by the Romans two thousand years ago, and some of our views and measures probably date back to the same period. No doubt a change of air, a visit to the baths of Baiae perhaps, rest and nutritious diet were the regimen for the Roman recovering from a plasmodial fever. No doubt he was ordered a goblet of Falernian wine with his meals and to his diet were added such delicacies of the Romans of that day as the delicious orange colored mushroom, the Amanita caesarea.

Hippocrates, Galen and Celsus made reference to the regulation of diet and exercise for the patient convalescing from acute disease. Today we think of the problem in much the same terms.

Our current writings contain little mention of convalescence. Houston's book, "The Art of Treatment," does not mention the problem of convalescent care. In Beckman's fine book on Treatment, the word, convalescence, does not appear in the index and a review of the Index Medicus reveals few articles of scientific value in this field. In Volume VII of Nelson's Loose Leaf Medicine an excellent article by Corwin on Convalescent Homes will appear which will give us the historical background of the whole subject; but he points out, and quotes others to the same end, that there is a lamentable lack of real factual knowledge concerning the conditions which exist in the convalescent individual himself.

The reasons for this ignorance are many and are easy to discover—three seem to me to be the more important. First, is an overemphasis on the psychological aspects of convalescence; second, a natural falling off of interest once the patient seems to be convalescing; and third, the grouping together under one term, convalescence, of a great variety of different states arising from many different diseases, emotional shocks, or surgical operations. Let us briefly comment on these three features.

* Read November 9, 1939 at The New York Academy of Medicine in the Conference on Convalescent Care.

For many years it has been the habit to attribute many or even most of the phenomena of convalescence to psychological causes. For example, Dunbar,[1] in 1936, quotes an eminent psychiatrist to the effect that 50 per cent of the problems of the acute stage of disease and 75 per cent of those of convalescence "have their primary origin not in the body but in the mind of the patient." This may be true but of course we recognize that this use of the word mind is a concession to ordinary usage, for the mind in the final analysis is but a functional expression of the body. If it is true that 75 per cent of the problems of convalescence arise in the mind of the patient, then our present methods are perhaps satisfactory; but if this is not true and we assume it to be, then certainly we will fail to investigate the convalescent state and will certainly not discover whatever underlying causes there may be for the phenomena of convalescence.

There is some analogy between this situation with regard to the convalescent state and that of psychiatry until very recent years. Just consider for a moment how the discovery of malarial therapy for dementia paralytica affected our conceptions. As Burlingame[2] recently wrote, "at one fell swoop a dozen different so-called mental diseases had a segment sliced off them."

Just as long as we considered the phenomena of mental disease to be of purely psychogenic origin, we failed to investigate the patient for possible organic diseases and we of course applied only such therapy as we thought appropriate for psychogenic disorders. Now today a new concept of mental disease is prevalent and we may hope for additional startling advances in therapy. An almost identical state of affairs exists with regard to convalescence.

The second point is that convalescence has, perhaps understandably, not interested the physician; the patient is out of danger, let nature take its course aided by a change of scene, rest, exercise, diet and tonics. This does not perhaps sound so important, but certainly we have been apathetic and careless about the matter and it is at this point that I wish to introduce my congratulations to The New York Academy of Medicine and to the Macy Foundation for coöperating in arranging this symposium—intended to focus attention on the problems of the forgotten man, the convalescent, and I suspect with the deliberate hope that our ignorance of the convalescent state will shame each of us into greater interest and active investigation of what may actually be the basic factors at

work in what we carelessly call convalescence.

The third point is an obvious one. We use the term, convalescence, to denote the period following such widely differing initial illnesses as lobar pneumonia, typhoid fever, duodenal ulcer hemorrhage, and also after such varied surgical procedures as thyroidectomy, herniotomy or acute appendicitis. The state of these patients as they come into what we call convalescence must obviously differ enormously—clearly their state is a function of a number of variables such as the previous condition of the patient, the duration of the illness, the degree of fever, and the disturbances of body physiology and chemistry incident to the disease. No two diseases can possibly leave the same state of affairs after the illness subsides and convalescence commences.

In a very rough way some cognizance is taken of this fact. We have rules of thumb permitting convalescents from some diseases a shorter period of inactivity than others and in a similar manner we stress certain needs in some—such as the restoration of lost weight, but too often the term, convalescence, is used as though it denoted a single entity—produced by a common cause, exhibiting common phenomena and amenable to a standard management. Obviously this is absurd and it would seem unnecessary to labor this point were it not for the frequency of the error and its seriousness. Not until we learn to recognize, in each type of convalescent, the actual abnormalities which persist from the preceding disorder and which differentiate that individual in convalescence from the same organism in health, can we properly meet the various therapeutic indications in each instance.

What do we know about this phase of convalescence? Very little, must be the humiliating reply. The very word, convalesce, means to grow strong and this is clearly the purpose of convalescence, but unfortunately we know very little of what produces even this weakness from which we would have our patients recover. We have all experienced it and wondered at it, yet we find it difficult to explain. It is easy to attribute this weakness to fever, to long-standing undernutrition or to nervous exhaustion, whatever that may be, but it is a very variable phenomenon and sometimes extreme after a short attack of such an infection as influenza, for example. We need more information on this as well as on many other aspects of the convalescent state.

Let us mention some of the few facts which are known—more to raise questions for further discussion than for any other reason. It is

known that the body metabolism rises in fevers and, as DuBois has pointed out, the rise is quite uniformly proportional to the degree of fever and does not show the variability which might be anticipated from the clinical differences shown by different infections. Following the return to normal temperature, the metabolism drops sharply—and one, therefore, enters convalescence with a lowered metabolism. This is more marked after a long illness such as typhoid than after pneumonia, for example. There is little doubt that this phenomenon is related to the degree of undernutrition. The available figures were obtained years ago when the usual typhoid patient was extremely undernourished. The data is scarcely applicable today when the disease seems less severe and treatment includes a higher caloric intake. In the former type of typhoid patient, the metabolism rose as convalescence continued but for some time the typhoid convalescent, according to Svenson,[3] quoted by DuBois, used more oxygen for a given task than did a normal individual. With more liberal diets, the patient can be kept in nitrogen and weight equilibrium and usually be brought into convalescence in a far better state. This, of course, alters the whole question of the duration of convalescence.

When anemia is present in convalescence as, for example, following a hemorrhage from duodenal ulcer, the question of diet becomes of the greatest importance. Whipple's studies on regeneration of lost blood proteins reveal how dependent regeneration is on the character of the diet and how much any, even trifling, intercurrent infection handicaps the restoration of the blood to normal.

Pneumonia is one of the few conditions in which studies of the disease have been continued into what may be termed the early days of convalescence. The data is quite extensive and demonstrates that during at least the early weeks of convalescence, marked alterations in body chemistry persist. After the crisis the concentrations in the blood of total base, chloride and protein require one or two weeks to return to their normal values; the chloride being slower than the others to reach its normal level. Sodium continues to be decreased while potassium is increased for some time after the crisis. The decrease in protein is due to a reduction in the albumin. Water is stored just before the crisis and lost soon after. Weight changes reflect this, but the changes in the electrolyte concentration cannot all be explained on fluid shifts, for the behavior of the freezing point indicates that abnormally high amounts of non-

electrolytes are present during the postcritical period.

These studies by Sunderman and Austin[4] at the University of Pennsylvania are indicative of the marked alteration of bodily chemistry which may be present in that period which we call convalescence. Obviously they must be of importance and yet we take no cognizance of their presence nor of any variability in the changes produced by one disease or another.

Similarly there is some evidence of disturbance of physiology persisting into convalescence after various fevers. After infection the pulse may be slow for several months and the blood pressure's reaction to exercise will afford evidence of the stage of convalescence (Mann[5]). The electrocardiogram may continue in convalescence to reveal evidences of myocardial damage (Köhler[6]).

In every field there is some evidence available which proves that the disturbance of the acute stage of the disease does not immediately disappear with the onset of convalescence. Reznikoff[7] has carefully reviewed the changes in the white cell hemogram from the end of the acute stage of an infection until complete restoration of health has occurred. The behavior of the various forms of white cells is fairly constant and is not understood. Why do the monocytes increase during the subsidence of an infection and the eosinophils rise after the infection is over? In the immunological field it is well known that the antibody titer continues to rise long into convalescence.

I mention these isolated facts to hint at the extent of the continuing disturbance which we might find if further studies were made in other lines and in other diseases. If one allows his imagination to replace facts it is easy to picture the various phenomena of convalescence as due to depression of various endocrine activities—a lowered adrenal reserve, a lessened gonadal activity, perhaps a general reduction in the influence of the pituitary, possibly the exact reverse—we do not know. Gastric acidity, histamine production, intestinal motility may all be abnormal for a longer period than one might expect.

In these days of powerful drugs and sera we must admit the possibility that their effects may not wear off as quickly as we might wish. The sulfanilamid-sulfapyridin group may be examples of this although their occasional toxic effects are usually prompt in appearance. Serum disease in mild form may occur as an unrecognized handicap to rapid convalescence.

In all of this, one must still not lose sight of the psychogenic aspects of convalescence, nor must we allow ourselves just because they have been overemphasized in the past to underestimate their importance in many cases. But we should look forward to the day when these psychological phenomena will be explainable in terms of abnormal chemistry and physiology. In the final analysis it may be nothing more than a difference in terminology, but it does seem to me that it is likely to discourage true progress if we accept the view that 75 per cent of the problems of convalescence arise in the mind rather than in the body.

Finally, a word about the treatment or care of the convalescent. We reveal our point of view when we speak of the treatment of a disease, but the care of the convalescent. As a rule, of course, the convalescent is not truly so unless he is on the way to complete health. Therefore, any detailed treatment may seem unnecessary. On the other hand, any treatment which may be administered is likely to get the credit for the almost inevitable improvement. In this manner, undoubtedly, did tonics and restoratives gain their reputation. Rest, increasing exercise, nutritious diet and a harmless tonic thrown in for good measure form the basis of most convalescent care. Obviously, however, if there are persisting deviations from normal in metabolism, bodily chemistry and physiology, restoration to health might well be expedited if attention were directed to correcting each and every one of these abnormalities. This would require much more knowledge than we now possess. The results of each disease, of surgery, of trauma, of emotional shock would have to be known and then individualized in each individual case.

The convalescent state can never be predicted from the disease alone. It will be influenced by the patient's sex, previous state of health, presence of other chronic diseases, temperament, et cetera. It must be different at different ages; in children, in adults, in the aged. And convalescent care will have to take these matters into consideration. The aged must avoid prolonged bed rest lest hypostasis result in pneumonitis; their habits must be respected for they cannot abruptly be altered. The aged patient must be accepted as he is whether the doctor likes it or not. He may well be damaged goods in a number of ways and one can hope only to restore him to his habitual best health level. Convalescence for the woman may differ widely from that of a man; that of an individual with pre-existing diabetes or tuberculosis must be altered to meet the special conditions.

In these brief remarks I have stressed what we all know to be true: that convalescence is not a constant nor a single state; that it presents many phenomena, many truly organic, some psychogenic; that we know far too little of the organic results of different acute processes which persist into convalescence; that ideal treatment of convalescence calls for the recognition of these deviations from the normal and for their correction in terms of the individual convalescent.

In the discussions which are to follow much data toward these ends will no doubt be presented which will answer some of the questions which have been raised. Only by such discussion can the matter be advanced, and if in this way we can arrive at a clearer conception of convalescence, this well-planned conference will have well justified itself. Let us attempt in these discussions to avoid generalizations and preconceived notions, let us bring to bear on convalescence the same factual and critical approach which has solved so many of our medical problems and which has been the secret of all great advance in science.

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CONVALESCENCE OF OLD-AGE PATIENTS

LEWELLYS F. BARKER

THIS Conference places emphasis upon a subject that has been too much neglected, namely convalescent care. And of all patients who are attended by physicians, it would seem probable that those of the old age group have been considered least, not only in regard to convalescence from disease but also as to the general medical problems of the elderly. Very few specialists on the diseases of old age have as yet been developed and knowledge of geriatrics should advance as pediatrics has done if we are to be supplied with expert gerontologists as well as with competent pediatricians. In 1930 there were about twelve million children under 5 years of age in this country and some six and a half million persons over 65 years of age. But the ratio of young to old is undergoing rapid change owing to restriction of immigration, to the rapid decline in the birth rate, and to the great increase in life expectancy due to curative and preventive medicine; in the two decades between 1910 and 1930, average life expectancy was increased by about 13½ years for each of the sexes—a hitherto unprecedented rapidity of advance. By 1935 the life expectancy of the general population at birth had risen to over 61 years. Unless present trends change it seems probable that by 1975 there will not be more than six and a half million children under five but there may be 30 million over sixty and perhaps 22 million persons over 65 years of age in the United States (E. P. Wilson). Though obviously intensive work in pediatrics will continue to be necessary, the importance of increased work (both intensive and extensive) in geriatrics during the decades just ahead of us can scarcely be overemphasized. The need was early foreseen by Dr. I. L. Nascher (sometimes spoken of as "the father of geriatrics") who published an important treatise on the subject in 1914, the introduction to which was written by the late Dr. A. Jacobi.

Physiological or natural old age in which the major involution goes on very gradually is highly desirable, but pathological or abnormal old

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age with premature breakdown of one or more organs or organ-systems is often a curse rather than a blessing. To quote Alexis Carrel, "added years without health and strength would be a calamity. . . . The number of centenarians must not be augmented until we can prevent intellectual and moral decay and also the lingering diseases of old age."

The diseases of later life differ in incidence, in symptomatology, in complicating processes, and in treatment from those of earlier life. As to incidence, diseases of the circulatory apparatus predominate, but diseases of the nervous, locomotor, digestive, and urogenital systems are also common.

Many diseases met with in advanced life do not occur among the young, or only exceptionally. Osteoporosis, Paget's disease, malum coxae, intestinal diverticulosis, prostatic hypertrophy, Parkinson's disease and cerebral arteriosclerosis are examples that one immediately recalls. On the other hand, the old remain free from a whole series of infectious processes since immunity has been gained to them in earlier life, though in the aged there is a peculiar tendency to develop certain suppurative processes of the serous membranes, biliary tract, urogenital tract and ear, often followed by general sepsis.

The symptoms of disease in the old may differ from those in the young. Thus, pneumonia may be afebrile and appendicitis may exist without local pain; in old age as Rolleston has said "the organs suffer in silence."

During convalescence from diseases in later life, complications frequently endanger life, those involving the heart or large blood-vessels being especially ominous; thus sudden unexpected collapse because of heart weakness may develop or a paroxysmal tachycardia may appear. In other cases we see gradual paralysis of the heart muscle, or we may be surprised by a venous thrombosis or an embolism. All the matters thus far referred to should be carefully borne in mind when we consider the especial subject of convalescence from disease among the old.

There is one disease common to youth which, as O. H. P. Pepper points out, shows no mercy to the aged, and that is whooping cough. Even if a person has had whooping cough as a child, he may lose immunity to it, catch the disease again from a child and die from it. For this reason the grandmother should not be called into service to care for a child with whooping cough.

Convalescence from Cardiovascular Diseases: The old saying that

"a man is as old as his arteries" and the clinical dictum that the systolic blood pressure in later life should be one hundred plus the age of the individual indicate the general recognition of the importance of circulatory changes in the old.

During recovery from diseases of the heart or blood-vessels after the fiftieth year of life, especial precautions should be taken. After an attack of coronary thrombosis, for example, the patient who has been given at first morphine (with a little atropine to protect the respiratory center) and who has been kept at absolute rest in bed for several weeks, should be permitted to return to activities only very gradually and then under the closest medical supervision. This is particularly true for persons who have been ambitious and overintense in their occupations and in the forms of recreation to which they have been accustomed. The physical and mental load that the person has earlier carried should be definitely reduced, and emotional excitement should be avoided. When occupation is resumed, it should be permitted for only an hour or two at a time at first, the hours of application being very gradually increased. The patient should be taught the importance of greater deliberation than formerly in the performance of his duties, the desirability of more frequent periods of rest and relaxation, and the value of gradually and systematically increased intervals of forms of recreations that are enjoyable but that do not throw any sudden or unusual strain upon the heart.

Similar precautions should be observed by elderly patients with increased blood pressure who have had a vascular accident of one sort or another.

Such elderly convalescents are often very difficult to control. Accustomed to a full life earlier, they are all too prone to disdain the discretion urged upon them by their physicians. But if they attempt foolishly to resume careers of excessive activity, either physical or mental, they are all too likely to pay severe penalties in the form of sudden death or permanent invalidism for their ill-advised rashness.

After a hemiplegia due to cerebral thrombosis in an old person, the non-paralyzed side should have some exercise early, for otherwise it will become weak also, owing to degenerative neuritis and partial arterial thrombosis on that side (Burr and Camp, 1905).

In cardiovascular-renal disease in old people, dietetic and general hygienic regimes should be even stricter and more closely supervised

than in younger persons. In time such patients will succumb to myocardial insufficiency, coronary thrombosis, cerebral insults, or uremia, even when the greatest care has been exercised.

Convalescence from Pneumonia and Other Severe Infections: Many old people die of acute lobar pneumonia or of acute or subacute bronchopneumonia. Formerly these diseases were responsible for about one-eighth of all deaths among the aged. Dr. Osler used to speak of pneumonia as the "old man's friend", and commenting upon this disease in his famous text-book he says: "Taken off by it in an acute, short, not often painful illness, the old escape those 'cold gradations of decay' that make the last stage of all so distressing."

But with the advent of sulfapyridine treatment it now seems probable that pneumonia will be the cause of death in the old less frequently than formerly. But even if a pneumonic infection be overcome by this marvellous new drug, great care must be exercised during the period of convalescence. The heart especially should be guarded from strain either from physical effort or emotional excitement. The patient should not, however, be kept too long in the recumbent position after the temperature has become normal. It is better cautiously to allow sitting up in bed with a back-rest, and later in a chair beside the bed, the physician keeping careful watch of the behavior of the pulse, blood pressure and heart's action.

The diet should be restricted for several days, the fluid intake should not be too large, regular bowel movements should be secured, and restful sleep at night promoted. Later when activities are gradually resumed, precautions similar to those recommended during convalescence from cardiovascular diseases should be observed.

Convalescence from Operative Procedures: The old cannot always escape surgical operations though they should avoid them except when absolutely necessary, for the mortality after major operations increases by leaps and bounds after the fifty-fifth year of life, despite the fact that some aged persons tolerate serious major surgery fairly well. In the old, successful surgery depends in no small part upon proper preoperative study and postoperative care. Great advances in methods of producing anesthesia (especially local anesthesia and spinal anesthesia) now make fairly safe surgical operations upon older persons that with the use of the older anesthetic methods would have been most dangerous to life.

Cancer of the lip, tongue, breast, uterus, rectum and prostate should be promptly removed surgically if discovered early no matter how old the patient is. It is interesting that in middle life women suffer from cancer more often than do men whereas in the senium the total frequency of cancer is about the same in the two sexes, though cancer of single organs may be very unevenly distributed between the two sexes, cancer of the esophagus, sigmoid and rectum occurring chiefly in males, cancers of the gall bladder chiefly in females.

Instances of primary surgical emergency (for example, acute intestinal obstruction and strangulated hernia) may be met with in the old and then the surgeon dare not withhold the use of his life-saving knife. Prostatic obstruction may compel the urogenital surgeon to intervene; fortunately, with advances in prostatic surgery and the introduction of new methods, the risks of operations upon the prostate have in recent years been markedly diminished.

During convalescence from surgical operations great care should be exercised to prevent infections (especially colds, pneumonias, infection of the urinary tract and, of course, local infections of the operative wound itself). Should infections develop, they should be combatted promptly by the newer methods now available. The behavior of the heart, of the blood pressure, and of excretions by the kidneys and bowel should be closely watched. When the postoperative patient becomes ambulatory, he should be warned of the danger of slipping on polished floors, for a fall may cause fracture of the neck of the femur, a common and most unpleasant occurrence in old age. As soon after an operation as it is safe to do so, the patient should be permitted to sit up in bed and a little later to become ambulatory since recumbency over a long period is undesirable. When the time comes for the resumption of activities the same precautions recommended to be followed after pneumonia and after cardiovascular disturbances should be observed.

Senile Anorexia and Marasmus: Some loss of weight after sixty seems to occur normally, for the age of the "lean and slippered pantaloon" is being approached. But during convalescence from disease among the elderly, gradual loss of appetite and a feeling of repulsion for food with rapid loss of weight are ominous symptoms. Though the old person's consciousness may be clear and the dangers of abstention from food may be recognized by him, he will sometimes declare that it is impossible for him to take nourishment. Formerly, when such "senile anorexia"

developed physicians found themselves almost powerless and often the patient died from inanition. Today we can save many of them by isolating them temporarily from family and friends, maintaining bed-rest, and injecting subcutaneously five or ten units of protamine-zinc insulin twenty minutes before breakfast and before the evening meal. Under these measures, appetite will often return, a diet high in caloric value (including milk and cream) may be ingested, and weight will often increase quite rapidly.

The condition known as "senile marasmus" in which there is progressive wasting of the body accompanied by gradual exhaustion and impaired functional activity of the bodily organs has occasionally been described as occurring in old persons, but whether or not it should be classified as an independent syndrome is doubtful. Sydney Smith in 1837 said that "everybody has their favorite death; some delight in apoplexy, and others prefer marasmus." If I met with marasmus in an old person, I should treat it as I would "senile anorexia."

Special Hospital Wards and Convalescent Homes for Elderly Convalescent Patients. Such wards and homes may often be advantageously utilized for the temporary care of aged convalescents. When the active wards of hospitals are overcrowded the tendency is to discharge patients as early as possible in order to make room for others who are more severely ill, often to the great detriment of the convalescent patient who may need both medical and nursing supervision for a further period before being sent home. The use of such wards and homes when available should, however, not be abused; the patients should be kept in them only for the length of time necessary to make transfer to domiciliary care by the family physician reasonably safe, since some patients, finding residence in the convalescent home delightfully irresponsible, may be tempted to shirk the resumption of normal duties. Hospital social workers have done much to educate physicians regarding the importance of adequate opportunities for proper convalescence of patients who must leave the hospital before they are fit to return to normal life.

Vitamin Deficiencies During Convalescence. Many older persons limit their diets so greatly even when they feel well that they do not ingest a sufficient quantity of vitamins, but especially when they have been under treatment for diseases in which rigid dietetic measures have been enjoined (as in certain diseases of the gastrointestinal tract) they are all too likely to develop vitamin deficiencies. As age advances, vita-

mins are less well-absorbed and assimilated. This seems to be especially true of vitamin C which plays an important role in oxidation processes. The vaginitis that occurs in old women may depend upon lack of vitamin A. Alcoholic addicts are prone to eat too little and the so-called "alcoholic neuritis" that many of them exhibit is in reality not due to the toxic effect of the alcohol but to lack of vitamin B_1 (thiamin chloride) just as is the neuritis of beriberi. Complaints of regional pains, of absence of appetite and of weakness in old people will sometimes disappear like magic after a few daily hypodermic injections of 2 mg. of thiamin chloride. The turbidity of the crystalline lens (cataract) that so often appears in later life is ascribed by some to lack of vitamin C. In pellagrous districts lack of nicotinic acid (B_2) is important. The physician should, therefore, see to it that elderly patients (as well as all other patients) during convalescence receive an adequate supply of vitamins, especially vitamins A, B, C, and D. Percomorph oil, thiamin chloride, brewers' yeast tablets, nicotinic acid, ascorbic acid and viosterol are now everywhere available for supplementing diets deficient in these vitamins.

Mineral Deficiencies During Convalescence. In later life many persons fail to take enough calcium and phosphorus. During the World War food shortage in Germany and Austria was responsible for hunger osteomalacia due to insufficient protein, calcium and phosphorus ingestion. Older persons require an intake of 520 mgm. calcium and 1200 mgm. phosphorus daily for the maintenance of calcium-phosphorus equilibrium.

Hormone Deficiencies During Convalescence. In some older patients, evidence of hormone deficiencies may appear and demand an extraneous supply. In convalescence from the menopause in women and at the time of the "grand climacteric" in men, the administration of sex hormones is sometimes useful. Especially in patients who develop anxieties, depressions and hypochondriacal ideas at this time of life, testosterone propionate has been found beneficial. A 1 cc. ampoule containing 5 mgm. of testosterone proprionate in oily solution is injected intramuscularly twice a week for four weeks, after which a 1 cc. ampoule containing 10 mgm. is given twice a week for two weeks. Doses as large as 25 mgm. have been recommended in severer cases. The hormone-ester is not given for its aphrodisiac effect (it may not have any) but for its general regulatory influence upon the disturbed endocrine system, and as a supplement to the psychotherapeutic measures used.

Though octogenarian and even nonagenarian paternity may occasionally be possible, sex desire should as a rule be sublimated in later life. Diminishing libido and potentia are physiological and desirable, though it is sometimes a cause of worry especially in older men. Attempts at so-called rejuvenation should be discouraged.

Several years ago Boothby and his associates at the Mayo Clinic showed that the speed of metabolism gradually lessens with advancing years. It is not surprising therefore that hypothyroidism is not uncommon in later life, manifesting itself by lethargy, slowing of thought, a tendency to drowsiness, preternatural susceptibility to cold, dryness of the skin, obesity and a lowered basal metabolic rate. When it is discovered, enough thyroid substance should be cautiously given to restore the basal metabolic rate to normal levels. Elderly patients with coronary disease or congestive heart failure, however, do not tolerate the use of thyroid substance well, even in small doses.

Diabetes in the old requires the use of insulin, but this too should be given very cautiously, watching closely any bad effect upon the efficiency of the heart muscle. The diet of elderly diabetics should not be too rigidly restricted.

Psychotherapy of Aged Convalescents. Young people often have difficulty in understanding the mental and emotional states of older people and young physicians may be less suited to the psychotherapy of the old than are doctors who, wearing perhaps the "silver livery of age," have themselves, through nature, education and time, happily matched a senescent maturity of judgment with a youthful vigor of imagination. The mentality of normal old age can scarcely be well understood except by those who have lived to be old, and have themselves remained healthy. There is greater need for understanding, gentleness, and sympathy on the part of the physician in the care of the aged than even in the care of younger persons.

It should be remembered that old people rarely wish to die; on the contrary, the majority of them hope to live on and on. As they grow older, certain mental changes are more or less characteristic. All the senses gradually become less acute though abnormal sensations are often complained of. Old memories may be well retained but the memory for recent events tends progressively to fail. Again, the old tend to fixity of habits and to dislike of change; they are prone to exhibit a kind of mental rigidity and to become self centered; character traits that they

may have shown in earlier life (such as anxiety, fear, depression, or desire of acquisition) may become ever more pronounced. Emotional reactions are likely to be less well controlled than in middle life. Finally, judgment may become impaired and the behavior may become such as to indicate "a lack of reflective and inhibitory control," so that a conservator may have to be legally appointed for the protection of the welfare both of the patient himself and of his family.

No small part of the mental ills of old age is referable to our faulty social, professional and industrial organization. We seem almost to have taken for granted that after sixty or sixty-five man must cease to be useful and should be "laid on the shelf." Moreover, the idea is too prevalent that most of the infirmities of old age are inevitable and irremediable. The age limit in the civil services takes no account of individual variations in capacity in later life; when the arbitrary age limit has been reached, a man or woman is thrown into the discard, willy-nilly. Through such compulsory retirement, the civil services, in many instances, suffer grievous and unnecessary loss. In many industries, a man of forty is already considered old, and if he loses his job he may find great difficulty in securing other employment. If such a man is no longer equal to the speed-up processes of certain industries, it should be possible to transfer him to an occupation for which he is still suitable. Think of the depressing effect upon a human being that must result when he is given to understand that he can no longer be useful and independent, when he knows full well that he could be if given a fair chance. The situation of the aged is a factor that dare not be overlooked in convalescence.

Depression and discouragement will do far more toward ageing a person than will normal living. Tell a man or a woman who has reached a certain age that retirement from life is compulsory, and you exert the most powerful influence toward making that person grow old rapidly and dangerously and often you shorten the life. Let us remember the great achievements of some persons when they were old—of Sophocles at ninety, of Titian at ninety-nine, of Benjamin Franklin at eighty, of Oliver Wendell Holmes at eighty, of Thomas Edison at eighty, of Paul Shorey at seventy-five, of Elihu Root at ninety and of W. H. Welch at eighty. Should such men have been compelled to retire at sixty-four while they could profitably continue some form of the work to which they had given their energies in earlier life? Should all members of the

Supreme Court of the United States be required to retire at seventy? I do not think so, and I find it difficult to understand how any one could believe that the United States would have been better off without the services of Chief Justice Hughes and other distinguished Justices of that Court who remained efficient in their work long after the age of seventy. No definite chronological age can be safely predicted as the time for retirement, or for sudden and marked reduction of activities; the matter is individual and personal.

The problems of suitable employment for all persons who can in any way be socially useful in their old age must be worked out. We must find out how to keep them engaged in the activities of which they are still capable, how to utilize the skills they still possess, and how to maintain their morale and their feelings of independence and happiness. Any tendency to narrow the horizon of interests to the immediate environment should be fought.

An attempt has been made to provide for the social security of the aged by giving some money to those who are not gainfully employed. But a little money is not all that the old really need. The other needs to which I have referred are even more important.

That serious unrest is developing among the older people of the country is shown by the political campaigns recently carried on in California and Ohio for "Thirty Dollars Every Thursday" and similar pension plans. These campaigns have just met with defeat; the general public recognized that they are economically unsound and would be followed by disastrous effects upon old as well as young. But unless our people solve the occupational problems of old age along the lines I have hinted at, elderly voters will, in the coming years, form such a large proportion of the whole electorate that they will be able to bring enormous pressure upon State legislatures and upon Congress. Let us hope that those with adequate foresight will be able to educate the American people to see that these old-age problems must be attacked scientifically and that rational measures are devised and instituted before it is too late.

In utilizing psychotherapy for old people during convalescence, a recognition by physicians of the situation in which old people find themselves is of the first importance. We must teach them that the world still needs them, their skills, their knowledge and their wisdom and that they should not deplore too much the loss of some of their powers but should be thankful for those that remain and continue to

make use of them. "Be your age and like it" is sound advice for the ageing person. Each old person, if he has lived hygienically in earlier life, may find senescence "as a lusty winter, frosty but kindly."

If the physician, the nurse, and members of the family will make the old person feel that they have a genuine liking for him and will seek his advice and help on various matters, his morale will be heightened. If he be made to feel that he is of no use and only a burden to others, he is apt to deteriorate rapidly and will lose interest in his appearance, his attire, and his personal cleanliness because he thinks no one cares for him. Lucky is the elderly man who has a loving wife who insists upon having his clothes pressed and cleaned regularly, upon his wearing clean linen and upon having him make regular visits to the barber and manicurist. The older woman can set a good example by maintaining interest in her own personal appearance and by making frequent visits to the hair-dresser for a wave. If she is told how well she looks she will prize the favorable recognition and will feel that somebody cares for her.

After age prevents participation in more strenuous forms of exercise and recreation, milder forms should be encouraged and persisted in. Recreation and enjoyment have their place in the life of all. No longer able to play tennis or hand-ball, perhaps, gardening, country life, croquet, or nine holes of golf on a course that is not too hilly may still be pleasurable. Music, the theater, the cinema, church activities or travel may be a boon to many. Companionship should be maintained by playing bridge or other card games, baccarat and dominoes. During hours when the old must be alone they may enjoy reading, painting, crossword puzzles, and the radio. Older women enjoy sewing and knitting; the gift of an electric sewing machine may be a godsend to a grandmother. Older people enjoy reminiscence and some may well be urged to write their autobiographies even if they are not to be published. Hobbies should be cultivated and sometimes can be made remunerative. Children and grandchildren when they are considerate can be a source of great joy to older people, who should be made to feel that they are still of service to their families. Family life is far better for the aged than institutional life though unfortunately the latter sometimes becomes necessary. Doctors and nurses who have sympathy, tact and good common sense and who will bear all these facts in mind can be of untold psychotherapeutic help to the old during convalescence from disease.

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RECENT ACCESSIONS

"Possession does not imply approval"

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Leipzig, Heft 1, 1938.

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Chicago, Vol. 1, No. 1, June 1938.

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Archivio italiano di medicina sperimentale. Torino.

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Bulletin sanitaire de l'Algérie. Alger.

Bulletins et mémoires de la Société roumaine d'endocrinologie. Bucarest.

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Deutsches Ärzteblatt. Berlin.
International Review of Recent Advances in Medicine (Washington Institute of Medicine). Washington.
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Journal of the Association of Medical Students. New York.
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Memorias do Instituto biologico Ezequiel Dias. Belo Horizonte, Brasil.
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Rivista di parassitologia. Roma.
Skandinavisk veterinär-tidskrift. Uppsala; Stockholm.
University of Minnesota Medical School Digest. Minneapolis.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

DECEMBER 7—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Election of Academy officers. ¶ Papers of the evening—Disorders of the venous and lymphatic systems—a] The participation of the lymphatics in acute and chronic inflammations, Cecil K. Drinker, Dean and Professor of Physiology, Harvard University Medical School; b] Clinical aspects with respect to the venous system, Bayard T. Horton, Associate Professor of Medicine, Mayo Foundation; c] Surgical considerations, Gerald H. Pratt, Assistant Surgeon, New York Post-Graduate Medical School and Hospital.

DECEMBER 21—*The Harvey Society (in affiliation with The New York Academy of Medicine).* Third Lecture, The Host-Parasite Relationship with Particular Reference to Heterogeneous Infection Chains, K. F. Meyer, Director, Hooper Foundation for Medical Research and Professor of Bacteriology, University of California.

SECTION MEETINGS

DECEMBER 1—*Surgery.* Reading of the minutes. ¶ Presentation of cases—a] Traumatic perforation of the rectosigmoid (two cases), David M. Weeks; Discussion by Guilford Dudley; b] Advanced carcinoma of rectum and perineum treated by electrical coagulation, Tibor de Cholnoky; Discussion by John C. A. Gerster; c] Wreden-Stone operation for anal incontinence (three cases), Lester Breidenbach. ¶ Papers of the evening—a] Wreden-Stone operation for anal incontinence, Lester Breidenbach, H. Lynn Wilson; Discussion by Frank Berry; b] Lymphogranuloma venereum, clinical aspects and treatment, Arthur W. Grace; Discussion by Borris A. Kornblith (by invitation); c] Adenomata of the sigmoid and rectum, Frank C. Yeomans; Discussion by A. W. Martin Marino. ¶ General discussion. ¶ Executive session.

DECEMBER 5—*Dermatology and Syphilology.* Presentation of cases—a] Mt. Sinai Hospital; b] Miscellaneous cases. ¶ General discussion. ¶ Executive session.

Pediatrics. The meeting of this Section did not take place on the regular date. Instead, the Section held a combined meeting with the Section of Medicine on December 19.

DECEMBER 12—*Neurology and Psychiatry.* Reading of the minutes. ¶ Papers of the evening—a] The masked personality of the Parkinson patient, Irving J. Sands; Discussion by Henry Alsop Riley, I. S. Wechsler, George H. Hyslop, M. Neustaedter; b] A study of 100 patients with psychosis with cerebral arteriosclerosis, Hollis E. Clow (by invitation); Discussion by Nolan D. C. Lewis, Louis Casamajor, C. Cheney, Karl M. Bowman, S. Bernard Wortis; c] Temperature and brain metabolism, Harold E. Himwich (by invitation), Karl M. Bowman, Walter Goldfarb (by invitation), Joseph F. Fazekas (by invitation); Discussion by S. Bernard Wortis, Nolan D. C. Lewis, Karl M. Bowman, Manfred Sakel.

DECEMBER 13 — *Genito-Urinary Surgery.* Reading of the minutes. ¶ Papers of the evening—Symposium on nephrolithiasis —a] A study of calcium and phosphorus excretion in nephrolithiasis patients, Reuben H. Flocks, College of Medicine, Iowa University (by invitation); b] Hyperparathyroidism in relation to urinary calculus, Richard Chute, Massachusetts General Hospital (by invitation); c] The conservative operative treatment of staghorn and bilateral calculus (motion picture demonstration), James T. Priestley, Mayo Clinic (by invitation). ¶ General discussion by A. R. Stevens, George F. Cahill. ¶ Executive session.

DECEMBER 15—*Orthopedic Surgery.* Reading of the minutes. ¶ Papers of the evening —a] A conservative therapy for fracture of os calcis (moving pictures), Otto Hermann, Boston (by invitation); Discussion by Robert Kennedy; b] Compound injuries to the hand, Henry Marble, Boston (by invitation); Discussion by Hugh Auchincloss. ¶ General discussion. ¶ Executive session.

DECEMBER 18 — *Ophthalmology.* Instruction hour 7:00 to 8:00—Orthoptic training methods, Le Grand H. Hardy; Demonstration 8:00 to 8:30 — Technique of measuring dark adaptation, Simon Shlaer, Ph.D., Columbia University (by invitation), Joseph Mandelbaum (by invitation). ¶ Reading of the minutes. ¶ Presentation of cases—a] Bilateral subconjunctival tumor, Albert Saradarian (by invitation); b] Vaccinal disciform keratitis following accidental inoculation of the lids; c] Sensitivity to nupercaine, Charles A. Perera. ¶ Papers of the evening—a] Vitamin A and vision, Selig Hecht, Ph.D., Columbia University (by invitation); Discussion by Robb MacDonald, Philadelphia (by invitation); b] The clinical aspects of vitamin A and dark adaptation, Francis Heed Adler, Philadelphia (by invitation). ¶ General discussion. ¶ Executive session.

DECEMBER 19 — *Combined meeting of the Section of Medicine and the Section of Pediatrics.* Reading of the minutes. Papers of the evening—The evolution of bronchiectasis in childhood and adult life, Clinical features and treatment—a] In children, Edith M. Lincoln; b] In adults, J. Burns Amberson; c] Surgical treatment, Frank B. Berry; Discussion by James Alexander Miller, John V. Bohrer. ¶ General discussion.

DECEMBER 20—*Otolaryngology.* Reading of the minutes. ¶ Papers of the evening— a] St. Vincent's Hospital, Pharyngo-maxillary fossa infection, Diagnosis and treatment (Lantern slides), Raymond J. Gaffney (by invitation); b] Roosevelt Hospital, The use of colloidal thorium dioxide in roentgenography of the paranasal sinuses, Russell C. Grove; c] Mt. Sinai Hospital—1. Meningitis and temporal lobe abscess secondary to suppurated petrositis, Clinical course with sulfanilamide, Eugene R. Snyder (by invitation); 2. Cerebrospinal fluid rhinorrhea, Pathologic findings, Max L. Som (by invitation); d] Presbyterian Hospital, Polypoid tumor of the esophagus,

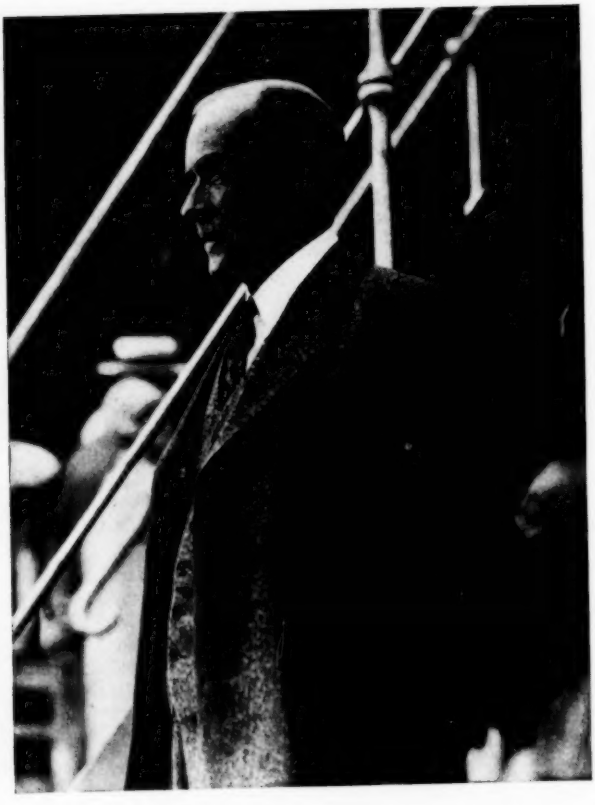
Report of two cases, Joseph J. Mahoney (by invitation); e] New York Hospital, Two cases of esophageal foreign body with complications, Fernand Vistreich (by invitation); f] Manhattan Eye, Ear and Throat Hospital, Osteogenic fibrosarcoma of the temporal bone, Harold W. Corya (by invitation); g] Post-Graduate Hospital, Clinical course of a temporosphenoidal lobe abscess in a ten-year-old child, Operative procedure and recovery, David L. Poe (by invitation). ¶ Discussion.

DECEMBER 26—*Obstetrics and Gynecology.* Reading of the minutes—Program by the Lying-In Hospital of the New York Hospital. ¶ Presentation of cases—a] Placenta accreta, Herbert F. Traut; b] Ureterovaginal fistula, Gerard del Junco (by invitation). ¶ Papers of the evening—a] Weight changes in pregnancy and the puerperium, John B. Pastore (by invitation); Discussion by James A. Harrar (by invitation) b] Hyperthyroidism in pregnancy, Carl T. Javert (by invitation); Discussion by R. Gordon Douglas (by invitation).

AFFILIATED SOCIETIES

DECEMBER 18—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Papers of the evening—a] Cases of hypernephroma with unusual clinical features, Louis E. Zaretski (by invitation); b] The role of radiotherapy in teratoma of the ovary, William Harris, Paul Klemperer (by invitation); c] Symposium on the small intestine—1. The Roentgen diagnosis of regional ileitis, S. J. Goldfarb (by invitation); 2. Atypical regional ileitis, B. B. Crohn (by invitation); 3. In nutritional deficiencies, David Adlersberg (by invitation); 4. In certain non-organic conditions, Marcy Lee Sussman. ¶ Discussion. ¶ Executive session.

DECEMBER 28—*The New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case reports—a] Congenital anomalies of coronary arteries with cardiac hypertrophy in infants, Beryl H. Paige, Babies Hospital; b] Acute hemolytic anemia and nephrosis caused by sulfapyridine, J. M. Ravid, Israel Zion Hospital. ¶ Papers of the evening—a] Vascular lesions in scleroderma, Abou D. Pollack, Mount Sinai Hospital; b] Pathology at the Peiping Union Medical College, C. H. Hu (by invitation), Peiping, China. Executive session.



LIVINGSTON FARRAND

1867 - 1939

IN MEMORIAM

Livingston Farrand

The death of Dr. Livingston Farrand has removed one who can ill be spared. His record is one of achievement after achievement. It is difficult to think of him except as the head of something. The long list of his honors and positions of responsibility has been printed and further expressions of appreciation from many sources will be heard in the Academy before this appears.

Starting his active life as an Instructor of Psychology at Columbia University, he proved that "the best way to learn is to teach." He was his own most brilliant pupil, for his practical psychology was one of the strong features of his active career. He was a keen judge of men individually, and rarely made a mistake; and he was also a keen judge of the effects of actions upon people in general.

His first activity in the promotion of public health—for in this field he will be longest remembered—was Executive Secretary of the newly formed National Association for the Study and Prevention of Tuberculosis. His quick grasp of its possibilities and problems, and his ability to bring together men and women in different walks of life, not accustomed to working together, made it possible to build up one of the strongest national health organizations in this country, which will remain a monument to his wise, far-sighted judgment in its earliest years.

In France his task as the head of the Rockefeller Commission for the Prevention of Tuberculosis called for rare judgment and rare tact. By sheer ability and powers of persuasion he developed and sold to the French people the American idea of the prevention of tuberculosis. The French Government bestowed the Medal of Officer of the Legion of Honor upon many Americans during and after the War, but to none more worthy of it than Dr. Farrand.

In becoming the chairman of the American Red Cross, he faced another big problem. Hundreds of local organizations which had been working at wartime fever-heat, had to be guided to continue those activities on a peacetime basis, and along other lines, and here again the same cool judgment, far-sighted vision, and powers of persuasion were powerful factors in that reorganization.

As President of Cornell, he was indefatigable in his efforts to develop the big program of the University, especially in the field of medical education and public health. He aroused the interest and enthusiasm of its graduates as few other presidents have. Probably no president was ever known personally more widely by his Alumni than Dr. Farrand. While he was President, his energy and endurance were boundless. He would often motor from Ithaca to catch a night train to New York, spend the next day at meetings and conferences with groups of his Trustees, and at the end of the day drop in at the University Club, relax for a brief time with his friends, and then take the night train back again to Ithaca.

In all his activities his work was thoroughly organized. His day was planned and, while he worked steadily, he conserved his energy. The quickness with which he grasped a situation was striking and once interested in anything he never forgot it. He was always accessible to any group in difficulties, and his advice and help were always prompt and valuable, and often called for.

Of all the honors which were showered on him, three, or perhaps four, stand out especially. The first was the Doctorate of Laws conferred upon him by his own Alma Mater, for Princeton is not lavish with honorary degrees to her own graduates. A second was the action of the French Govern-

ment in making him a *Commander* of the Legion of Honor nearly twenty years after he had left France. A third was his election as a Governor of the New York Hospital, the first physician in one hundred and twenty years to become a governor. Only four others have ever held that position, two being residents of London, Drs. Fothergill and Lettsom, who had been helpful in the founding or in the early days of the Hospital, a third, Dr. Samuel Bard, whose earnest appeal in 1770 was responsible for the founding of the Hospital, and Dr. Hugh Williamson, a philosopher and philanthropist. The fourth might well be his appointment as the first President Emeritus of Cornell.

With all his honors and high positions Dr. Farrand never changed. Simple, companionable, sympathetic, to his host of friends he was always "Tony Farrand," always a welcome addition to any gathering, more interested in what the others were doing than in discussing his own work; with a quick sense of humor and an alert mind he was a delightful raconteur. He was an ardent and expert fisherman, and he fished as hard as he worked whenever he got the chance.

When he reached the age of seventy, he retired as President of Cornell and was besieged by offers to undertake constructive and important work from many sides. Keen in mind and vigorous in action, he worked hard and constructively until the very end, just as he would have chosen.

He has left a great void. His place will have to be occupied, and filled if possible, but Kipling's words will have to be modified: it will take more than *one* man to fill Dr. Livingston Farrand's place.

PHILIP VAN INGEN.